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ENDOCRINOLOGY:

The BULLETIN of the ASSOCIATION for the STUDY of INTERNAL SECRETIONS.

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THE LITERATURE ON THE INTERNAL SECRETIONS. Containing 123 Titles and Articles Reviewed

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"In this last class, dysmenorrhea should be especially included. In my own practice I have observed, in a truly extraordinary manner, the cure or relief of many such cases through the medium of this type of organotherapy. My best results, however, have been gained in the administration of corpus luteum for the relief of the severe nervous symptoms attendant upon the menopause of both the physiological and artificial varieties and the functional amenorrhea of young women."—Dr. Adam P. Leighton, Jr., The American Journal of Obstetrics and Diseases of Women and Children, November, 1915, page 878.

"Mrs. P. D., aged 35, married twelve years was the mother of six children. Menstruation was regular. She complained of nervousness, irritability, inability to carry on the household duties, and depression. All symptoms were worse at the menstrual period. This patient was first seen in October, 1911. To nine-tablet doses per diem she responded at once; reported that she had not felt so well in years. After one month of this treatment the dosage was reduced to three tablets a day and continued another month. She then gave it up altogether, and is still feeling perfectly well."—Dr. Curtis F. Burnam, The Journal, August 31, 1912, page 698.

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ENDOCRINOLOGY:

The BULLETIN of the ASSOCIATION for the STUDY of INTERNAL SECRETIONS

JULY—SEPTEMBER, 1918

A NEW PLURIGLANDULAR COMPENSATORY SYNDROME*

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INTRODUCTION

For the past six years there have come to my notice in my service at the Neurological Institute, New York City, as well as in private work, a fairly large number of cases in early adolescence whose chief complaint was great muscular fatigability. Usually combined with this outstanding symptom was headache referred to the frontal region and midway between the temples. Included in the history was frequently a statement of recent or concurrent rapid growth in height as well as of the extremities. Frequent repetition of these complaints in various individuals led me to go deeply into their antecedent history, their family history, and to follow the cases as carefully as possible during their course. Their clinical examinations also showed many character-

*Read in abstract at the second annual meeting of the Association for the Study of the Internal Secretions, Chicago, June 10, 1918.

istics in common, as did their laboratory and X-ray findings. Finally, one case, observed for six years, went through various stages to recovery at the age of thirty-two years. From his early history we recognized symptoms that are presented by cases observed from time to time in the beginning stages of this syndrome, notably the fatigability, the headaches, and the skeletal growth. "Cross Sections" at various stages of his further progress also resembled clinical pictures in different patients that had heretofore been somewhat puzzling to analyze.

In the past three years so many cases of the kind have been observed that from our past experience we have been enabled to foretell, to a degree, the progress that such cases would undergo in the future. To add to this assurance, of late it has been my privilege to see many individuals admitted to hospital for divers complaints of middle age, in whom were recognized the final compensatory stages of the syndrome here to be presented. Upon close questioning, their antecedent history bore out to surprising detail the facts that our studied clinical types presented to us in various stages of the syndrome. They were completely compensated cases and their presence in the hospital was for some entirely adventitious cause. So that our observation has netted us: (1) clinical types presented by single cases at various ages and stages of the syndrome; (2) progressive cases, observed over periods of from one to six years, showing the changing and probably compensatory nature of the disturbance; (3) completed cases in which the disturbance had come to a definite stop, in which the antecedent history bore out the close relationship to our isolated cases which were still in active progress;

(4) uncompleted cases in which the condition, after going through the several preliminary stages, remained indefinitely progressive. Manifestly, to complete the chain, it is necessary to observe at least one case from the beginning to the end of the disorder —a period varying from ten to twenty years. Until this can be done, we must fill in the gaps as best we can.

GENERAL DESCRIPTION

The syndrome, pieced together as above presented, may be generally described as beginning in youth some years before puberty and going through its varying stages in about two decades. In its incipiency (*first stage*) it presents largely the characteristics of the so-called status thymico-lymphaticus, or status hypoplasticus of Bartels. There is complaint of muscular fatigability as a subjective sign. Objectively the case presents frequently, though not invariably, (for exception see case Bryan, fig. 6) an insufficient genital development, with perhaps inversion of sex type with a penis that emerges from scrotal folds of labial type, or crytorchism or both. In the female, the menses are usually delayed, the uterus and ovaries remain infantile and there is scarcity of pubic hair. Blood pressure is usually low, and blood sugar content low. Enuresis is common. There is usually present, the white line of adrenal insufficiency of Sergent.

In the *second stage*, that beginning at puberty, we find a continuance of the muscular fatigability or even an increase. The genitals may remain backward in development, the pubic hair is sparse and has the distribution of the opposite sex, the male showing a horizontal demarcation. Axillary hair is absent

and chin and lip show no signs of hair in the boy. Blood sugar is low, usually below .070%, and blood pressure below the normal. The white adrenal line may be elicited, especially marked after fatiguing exercise. Roentgenograms of the skull usually show a sella turcica which is small or which may apparently be even enclosed by the clinoid processes. This is an important point to determine, for the later progress of the disorder presumably depends upon the capacity of the pituitary gland to become hyperplasic. This excessive function of the pituitary later on dominates the picture and is conducive to compensatory cure. The thymus gland frequently is seen in the X-ray quite enlarged. In some cases of extreme fatigability, I have also seen pineal shadows. During the second stage, rapid growth in length begins to become manifest,—not ordinary normal growth,—but rapid in the extreme so that 5 or 6 inches in height a year is frequent. With this growth, fatigability increases, and it is on this account that the case is first brought to our attention.

In the *third stage,* we begin to see the results of some of the compensatory activities. It is usually ushered in about the 20th year of life. Growth has continued until the patient is 6 feet high or over; his weakness, even though his musculature seems splendid, is his prominent symptom. He shaves rarely or never. Pubic and axillary hair remain as before. Now he begins to notice an enlargement of his hands and feet, and a frontal headache or rather an intratemporal headache comes on. Blood pressure remains low (90 to 100 millimetres systolic), blood sugar usually remains low, but now frequently rises as compensation progresses. Our patient shows decided

vagotonic symptoms. An X-ray of the skull at this stage, or during this stage, if the case progresses favorably, shows a sella turcica which, while small, may show erosion of the clinoids and a deepening of the cavity. This tendency of the pituitary to become hyperactive produces the headache (if the sella is contracted), the increase in blood sugar content, the growth of hands and feet, and a gradually rising blood pressure.

The *fourth stage* now comes on, from three to ten years later. This is the stage in which either complete compensation is produced or else the untreated case takes on the varying and various attributes produced by an enlarged pituitary body engrafted upon the earlier manifestations of a thymic state. That is, we have in the completely compensated case, features of acromegaly, although the blood-pressure and blood sugar are normal and the headaches have gone. The sella on X-ray seems large. In the uncompensated cases we usually see a sella which is still small and bridged, with headaches of increasing severity, perhaps attacks of *petit* or *grand mal,* mental torpor, increase of weight with constantly increasing fatigue and a final lethal termination in intercurrent disease.

A brief resume of the characteristic symptoms and findings in the different stages is here succinctly put forth:

First Stage. The bony structure shows various endocrine anomalies and defects; disproportion of various skeletal units; teeth late and epiphyses slow in joining shafts of bones; hyperextension of joints; hair growth late and sparse, distribution of invert type; cramps in muscles; tendency to hemophilia

and spasmophilia; enlarged thymus; tonsils large and adenoids; low blood pressure; low sugar content of blood; epistaxis; cyanosis of extremities; fatigability; small sella turcica; enuresis; low CO_2 coefficient of blood.

Second Stage. At about age of puberty; rapid skeletal growth begins; late menses and small or infantile uterus; great fatigability with all evidences of low adrenal supply—low blood sugar; low carbon dioxide combining power of the blood; white line of adrenal insufficiency; pubic hair of invert type; lack of hair on face and chin and axilla; smooth soft skin of child; genitals of invert type or else retarded; vagotonia; symptoms of hyperacidity and gastric ulcer; enuresis; undue length of long bones; low blood pressure; little stamina.

Third Stage. 20th to 30th year; beginning giantism; headaches pituitary in character; drowsiness; acromegalic beginnings or other pituitary stigmata; fatigability may continue or improve; mental confusion and hebetude; epileptiform attacks—uncinate in type; sella turcica enlarges or else erosion of sella or clinoids takes place; blood sugar gradually increases if cure established. In uncompensated cases mental symptoms, moral and intellectual deficiencies and delinquencies arise.

Fourth Stage. Either complete compensation—so that patient may live comfortably within limits of exertion or else progress to end of life as pituitary case. The various external manifestations of the pituitary disturbance remain even if physiological cure is complete. Blood pressure rises; headaches cease; fatigability vanishes.

DISCUSSION OF SYMPTOMATOLOGY

The bony structure in the first and second stages usually shows anomalies in proportionate skeletal growth, i. e., legs too long for thorax or vice versa; the joints usually are hyperextensible and frequently

the ligaments are so relaxed that dislocations are easily produced. The extremities can be thrown about like flails; while the teeth are usually delayed in their appearance they also show certain characteristics. The lateral incisors, especially in girls, are frequently greatly underdeveloped. The canines, likewise, are either underdeveloped or else take on the flat appearance of incisors, losing their fang-like appearance. With the cyanosis of the extremities we occasionally get a pustular-like eruption about the nails. The symptoms during the second stage may need some elucidation. The so-called "white line" of adrenal insufficiency was first described by Sergent. It has not been proven to be due to the deficiency, but in my experience it invariably accompanies low blood pressures, and may be made to disappear very quickly after a hypodermatic injection of adrenalin. Previous emotional disturbance, even so slight as that produced by standing before a camera to be photographed, will make its appearance impossible to obtain. It is obtained best by having the patient lying quietly in bed for a short while and then stroking the skin, preferably of the abdomen or thigh, lightly, with the palmar surface of the index finger. In 10 to 20 seconds, there will be a blanching of the skin thus stimulated. (See Sergent's article, Endocrinology, 1917, 1, 18, for the explanation of this phenomenon.) The low carbon dioxide combining power of the blood plasma diminishes the so-called "buffer" property of the blood and leads to acidosis on slight provocation. The smooth soft skin of these cases, even in the third decade of life, with little or no secondary hair on the face, a faint suspicion of lanugo on the lip and chin, and a "peaches and cream" com-

plexion, frequently stamps these cases at sight. The headaches, produced as will be discussed in the pathogenesis, are of a specific type. They are invariably stated to be between the temples, the patient indicating the locality by putting one index finger on each temple, directed mesially. We have come to call them "pituitary headaches." The vagotonia present in many of the cases frequently takes on the character of hyperacidity of the gastric juice with frequently symptoms of gastric ulcer, spastic constipation and eosinophilia. In the third stage, the symptoms of great interest are the mental ones. In many years' observation of pituitary disorders, we have been frequently struck with the mental quips of the hypopituitaric. He exhibits lack of inhibition of the emotions, becomes highly excitable on little cause, alternating with sluggishness; frequently has phobias and compulsions—(one case was a true kleptomaniac)—shows frequently moral and sexual obliquities; and exhibition of pituitary feeding often modifies these characteristics. The symptoms of the uncompensated cases usually merge into those of a frankly dyspituitary syndrome which it is not my province to discuss here.

AETIOLOGY

In practically all our cases, there have been family histories of importance as regards endocrinopathies. Frequently, parents or grandparents have shown such disturbances as diabetes, goitre or acromegaly. A very common complaint is giantism. Collateral branches, too, show similar disturbances. Thus, W. W. (fig. 10) the fully compensated case, has four cousins all afflicted with Graves' disease. There appeared in our cases no particular antecedent

disabling disease or injury. One case, now in the second stage, had two brothers, both dying suddenly after exertion without known cause, in youth—possibly a so-called thymic death.

DISCUSSION OF PATHOGENESIS

During the first stage, we see a clinical picture which is dominated by the characteristics of the status hypoplasticus of Bartels. The anomalies have been variously credited to hypofunction of the individual endocrine glands, excepting the thymus, which is supposedly hyperactive. Thus, Tandler and Gross and Tandler have described many of the features of such a condition due to deficiency of the gonads. Wiesel, Schur, and Schmorls and Ingiers have given both clinical descriptions and histological and pathological findings in such hypoplastic conditions referable to underactive or inhibited adrenal glands. Many observers have described the smallness of the sella turcica. My own observations agree with these. All of our cases show the smallness of the sella turcica in the early stages and in addition many of them have the bridging over by the clinoid processes, evident on X-ray examination. With these deficiencies of glandular structure and their diminished physiological activity *ab initio,* the organism would of necessity come to early grief if some corrective were not forthcoming. Many cases do succumb early. Undue exercise, sudden excitement, narcosis, are all critical moments for such organizations, many of which cannot survive them. After puberty should have been reached (the second stage) the deficiency of the gonadal inhibition to growth (Tandler and Gross) is responsible for the extreme height rapidly reached

by our cases. One of our cases (Private B.) however rather opposes this theory in that the gonadal system early became hyperplasic and still the growth in body took place. This excessive genital development may be due in his case to an early involution of the pineal gland, for in the X-ray, calcification of the pineal is seen. (Some authors hold that the overactive thymus with disturbed calcium metabolism is the cause of such "thymic giantism.") The deficient adrenal-chromaffin system is to be credited with the great fatigability, the low blood sugar content, the low blood pressure and the white line. Now comes the third stage, the all-important one. It is in this period that the outcome of the syndrome is determined. In our judgment it is the pituitary gland which is here the critical factor. As we have seen, it is invariably enclosed in a small sella turcica and possibly even hemmed in by the clinoids. Among its functions we have as all important, a blood pressor principle and a sugar mobilization factor. Both of these are deficient in our patient. If the pituitary possibly could become hyperplasic and hyperactive with an intensification of these important properties, compensation might be accomplished. Such tendency to hyperplasia in a small cavity would of necessity through pressure produce headaches—an invariable symptom in the third stage of the compensated cases. And such headache would continue until the enlarged gland through erosion of its bony capsule or through pushing apart the clinoids made sufficient room for itself. As will be seen, these headaches continued for two to three years in some of our cases. Synchronously with these headaches, other incidental features of an enlarged pituitary gland became manifest;—(a)

acromegaly—lasting until the headaches ceased and the process then likewise ceasing; (b) a higher blood sugar content; (c) a higher blood pressure; (d) a diminished sugar tolerance. To make this view of the nature of the process of compensation more tenable, many of the sellae turcicae of our patients in the second and third stages show erosion of anterior or posterior clinoid processes; and in the final stage, an enlarged sella with practically no clinoid processes left at all. In the cases in which no compensation was effected, i. e., in which fatigability, *et cetera,* remained and progressed, the sella showed no enlargement (notably that of T. R., fig. 12). In these cases, we had headaches, periodical in type, adiposity, mental and moral deficiencies, *petit mal* and other manifestations. Curiously enough in *all* our cases, the feeding of the pituitary gland in fairly large quantity, disposed of many and at times of *all* of these symptoms. But if the feeding were diminished or stopped, the symptoms reappeared. It seemed analogous to thyroid feeding in myxoedema. One case, which gave a typical early history and seems uncompensated today at the age of 44, still shows the very small sella turcica with a clinical picture of abnormal bony structure much resembling Paget's Disease. On pituitary feeding, this case is improving markedly in its features of fatigability, headaches and heaviness of extremities. It is too early to state whether in her case the cancellous condition of the bones will be restored. Finally, the fourth stage is ushered in by a gradual cessation of the fatigue, amelioration of the headaches, restoration of a normal blood pressure and normal sugar content of the blood. But the adventitious signs of the disturb-

ance of the pituitary gland remain. Thus the fully compensated cases may show acromegaly more or less marked; *and this acromegaly is not to be taken as a diseased condition needing treatment, but simply as the hallmark of a process that has come to a stop—a self-curative process.* It is analogous to the hypertrophied heart become so through the deficiency of the cardiac valves and making up for such deficiency by its enlargement. And that condition likewise, *per se,* needs no treatment. A case that presents acromegalic features, therefore, need not necessarily be a case that calls for therapeutic intervention. It may well be a "finished" case. (W. W. fig. 10) is a good representation of this type. These "finished" cases, must always, however, live within certain limits of exertion and stress. The cases that in the fourth stage do not spontaneously go to full compensation, are those in which we either find a sella turcica which did not enlarge (perhaps because there was no spontaneous effort of the pituitary to become hyperactive) or in which an enlargement of the sella did take place and the pituitary even in its hyperactive condition was not sufficient to compensate. These uncompensated cases go right on with progressive symptoms of fatigability, asthenia, headaches and so forth, making of them easy prey to intercurrent affections.

TREATMENT

The treatment of these cases in any stage is extremely satisfactory. The great point to remember is the probable nature of the process of compensation which the organism is endeavoring to carry out. That would make one believe that suprarenal gland therapy is indicated throughout on account of the patent deficiency of this organ in these cases. And

yet in our hands its administration is disappointing. The whole gland perhaps has given better results than adrenalin, although the latter, either hypodermatically or (even against the dictum of the physiologist that it is inert when administered per os) by mouth in larger doses is good to tide over exceptionally bad days of fatigue and exhaustion. But the prime agent—almost a specific one—is pituitary gland in some one of its varied forms. Whole gland feeding in fairly large doses, gr. ii to gr. iii t. i. d. may be given in appropriate cases. Occasionally, pituitrin hypodermically 0.50 to 1.00 c.c. per day or alternate days for one or at most two weeks at a time is excellent as supplementing the feeding of pituitary gland. Occasionally in cases with pronounced genital delay, anterior lobe pituitary gland gives fair results. In those cases with vagotonic symptoms, hyperacidity and conditions resembling gastric ulcer, atropine in doses to physiologic tolerance is indicated, and gives results. But the pituitary feeding in itself, alone, produces highly satisfactory improvement in almost every case. Under its use, the headaches disappear, the fatigability diminishes, the blood pressure and blood sugar content increase, and the case goes on to cure. Gradually the pituitary feeding can be diminshed and finally discontinued. In the older cases, in which the sella persists in remaining small (T. R. fig. 12) and (J. S. fig. 11) constant feeding would seem to be necessary; at all events, the patients relapse as soon as treatment is stopped. Indeed, the patients themselves reach that point of accuracy of judgment in feeding the gland to themselves that they can determine the size and frequency of the dosage necessary to maintain them comfortably.

The following case histories are cited as a few among many which show characteristics of the different stages of the syndrome. Only facts having direct bearing are introduced into the case histories.

FIG. 1

Fig. 1. J. M. Case 1. Shows abnormal length of thorax compared with legs. Thighs especially short compared with lower leg. Small genitals. Has large thymus and enclosed sella turcica.

Case 1. J. M. (fig. 1). Ten years; mentally backward; no hair on body anywhere; genitals undeveloped; elongated thorax; spasms in muscles; great

fatigability; is a bed wetter; joints are hyperextensible; has nose bleeds. X-ray of chest shows thymus (fig. 3); skull shows small sella turcica, entirely bridged over (fig. 2). Blood pressure 85; white adrenal line.

FIG. 2

Fig. 2. J. M. Case 1. Sella turcica small and entirely enclosed and "roofed in."

Discussion. This case is presented simply to show the type from which arise the cases presenting the later features of the syndrome and hence may be classed under stage 1.

Case 2. Master F. J. Age, 13½ years; height, 61½ inches. He was brought to the Neurological Institute on account of his predeliction for lying and further for his rapid fatigability. He had been discharged from several schools on account of his incorrigibility. The climax was reached when he

appeared as a material witness in a murder trial, his evidence being of the greatest importance in the conviction of the accused. Apart from these facts, he also complained of spasms in the muscles, especially

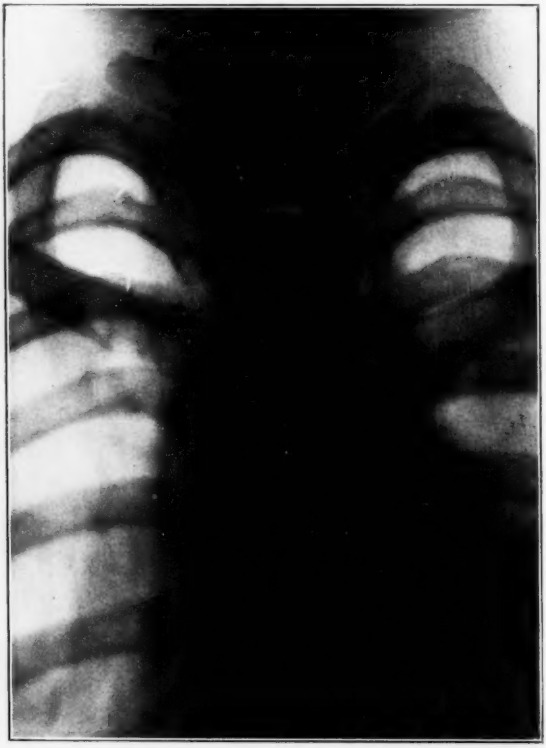

FIG. 3
Fig. 3. J. M. Case 1. Shows thymic enlargement.

of the calves, which occasionally awakened him by the pain caused thereby. He had frequently also had nocturnal enuresis. Upon stripping him (fig. 4) the examination revealed the following: the body was perfectly hairless, no trace of pubic or axillary hair

being evident. The genitals were small—infantile in fact—but both testicles were descended and the scrotum surrounded the penis like a labial fold. Upon eliciting the cremasteric reflex, however, the testicles

FIG. 4

Fig. 4. F. J. Case 2. Age 13½ years. Shows hypoplasia of genitals and a scrotal fold surrounding base of penis. Absence of hair. Bruise on raised arm from slight pressure.

were drawn up out of the scrotal sac into the inguinal canal where they could not be palpated. He bruises very easily, the dark patch on the left raised arm

being produced by the simple pressure of the examiner's thumb in raising the arm. Hands and feet are somewhat larger than they should be. Stroking the skin of the abdomen produced a marked white line of reaction, which persisted for a rather long time.

FIG. 5

Fig. 5. F. J. Case 2. Pituitary fossa shut in extremely by large clinoids.

His blood pressure was low, 80 mm. Mentally he was well up to his chronological age according to the Binet-Simon scale. Upon close questioning he admitted that he had frequent headaches referable to a point midway between the temples and deep-seated.

The neurological examination was negative. Laboratory examination showed the sugar content of the blood to be .070%. Otherwise blood and urine were negative and the Wassermann was negative. X-ray examination: The sella turcica (fig. 5) was small and encroached upon by large clinoids; the upper thorax showed a thymus shadow.

Discussion. This case is presumably a type of the beginning of the second stage of the syndrome. It presents many of the well marked features of a status hypoplasticus:—small sella, enlarged thymus, low blood pressure, low blood sugar, marked fatigability, spasmophiliac and hemophiliac attributes in addition to the obvious externals. The mental attributes are those which we frequently see in small and enclosed sellae turcicae. This case is presented simply as a living present example of the early beginnings of the second stage of the syndrome.

Case 3. Private B. (fig. 6). Age 20 years; height 6 feet 1 inch. This case was sent to the Institute by Capt. Reed, stationed at Fort Wood, to determine whether or not the man was a malingerer. His one complaint was that of excessive fatigability after moderate exertion. As a result he could not perform the military duties required of him. His musculature and his whole bearing and appearance when stripped were that of a powerfully and symmetrically built young giant, and seemed to belie his statement of rapid fatigue. His early history could not be obtained with any degree of reliability for, coming from a mountainous district of the South, he was extremely uncommunicative. In early adolescence he was a rover, traveling over many states in divers

occupations, but never steadily at any one. He did say that for the past three years he had been rapidly and steadily growing in height, that this growth was still continuing and with it his fatigability was

FIG. 6

Fig. 6. Private B. Case 3. Feminine distribution of pubic hair; large genitals; height 6 feet, 1 inch; no hair on face. Seems well-proportioned.

increasing. Stripped, he showed a splendid make-up muscularly. Of note was the fact that he had practically no hair on his lip or chin, no hair in the axillae, pubic hair of the feminine type and rather largely

developed genitals. Stroking the skin produced a white persisting reaction. His blood pressure was between 95 and 100 mm. systolic, 80 diastolic. Blood sugar was 0.062%. X-ray examination showed a

FIG. 7
Fig. 7. Private B. Case 3. Complete closing in of pituitary fossa.

sella turcica (fig. 7) which was extremely small, with thickened anterior and posterior clinoid processes completely roofing in the cavity. A shadow in the pineal region also was evident. The thorax showed a thymic shadow. Neurological examination was negative. Viscera appeared normal.

Discussion. This young man is going through the transition period from the second stage to the third. His low blood pressure, low blood sugar percentage (extreme normal low limit should be at least .075%), white skin reaction line, all go to prove his statement of fatigability. In addition he shows a crowded pituitary fossa and a pineal shadow. We

have found in the past two years in a large percentage of muscular dystrophies, pineal shadows; and in extreme cases of muscle fatigue in the adolescent, short of dystrophy, there were shadows in the pineal region. This parallelism between the myasthenic types and early involution of the pineal gland will be the subject of a future paper. This feature of the case is an example of many similar ones. But presumably early pineal involution also produced his enlarged genitals. He is undergoing the rapid growth incident to the second stage of the syndrome in spite of the fact of the enlarged genitals. Some authors (especially Tandler and Gross) have maintained that the hypoplasia of the genitals accounts for the continuance of the skeletal growth. That is certainly disproved here as a universality. Upon feeding of pituitary gland, this youth improved sufficiently to go back to army life. After the lapse of a few months, he discontinued this feeding and shortly thereafter returned with his old complaint of fatigability. He is again improving on treatment. No white line can now be elicited, and his blood pressure is usually at 120 mm.

Case 4. G. E. R. (fig. 8). Age 22 years; height 6 feet $3\frac{1}{2}$ inches; single; stenographer. Came to the Neurological Institute complaining of loss of memory and lack of sleep; feeling stuporous and extremely fatigued. Has headaches intratemporal in location. Not able to do much manual work on this account and hence took a position as stenographer. Is exempt from military duty, being the sole support of his mother.

Past History. While a child, he was never strong; he took a long time to develop and on account of his

ways—feminine—was always known as "sissy" to his playmates. He realized this appellation to be more or less just. Would easily cry if deprived of his

FIG. 8

Fig. 8. G. E. R. Case 4. Height 6 feet, 3½ inches; feminine pubic hair; no hair on face; musculature seems flabby; feminine attributes.

way and still does so. Always was a bed-wetter, and this weakness persisted to his 19th year. Realizing his feminine attributes, he endeavored to compensate for them by indulging in the most manly of sports—boxing and football. But he was too slow

to amount to anything here. He gave up this conflict and sank to his own recognized level—became a stenographer. He began to get headaches at 17 years of age, at which time his excessive growth started.

Examination. A man powerfully set-up, 6 feet 3½ inches high and proportionately built. (fig. 8.) No hair on face or body except in the pubic region, where it is of feminine distribution. The scrotum also is divided above the penis into typical labial folds. He shaves once in two weeks. His appearance is really

FIG. 9

Fig. 9. G. E. R. Case 4. Sella turcicæ with anterior cavity eroded and a deepening of posterior fossa.

pugnacious, but is not borne out by his mental attitude. He cries when questioned about the simplest difficulties. His blood pressure is 100 mm., systolic. He has the white line reaction of the skin, and his blood sugar was low. The X-ray of the skull shows

a sella in which erosion of the anterior clinoid is evident and an excavation of the posterior portion of the floor. (fig. 9.) The X-ray of the thorax shows a possible enlargement and persistence of the thymus. Neurological examination is negative.

Discussion. The early history is that of a thymus state. The further progress, especially the headache concomitant with the growth is suggestive of pituitary enlargement. This is partly borne out by the picture of the sella. His headaches are now much less prominent than they were, but his fatigability is marked. His growth seems to have ceased. This case belongs in the third stage—with the giantism gradually reaching its acme, with the stuporous and drowsy mental condition of a dyspituitaric still present, great fatigability, low blood pressure and low blood sugar content. The enlargement of the sella turcica however gives promise of a gradual efficient compensation taking place. Feeding of whole gland pituitary extract within two weeks measurably improved all his symptoms. It is still being continued.

Case 5. W. W., 32 years; machinist; married; several children; height 6 feet 4½ inches; acromegaly in slight degree. This case has been under our observation since 1912. At first the complaint was one of utter exhaustion to the exclusion of all minor ills. He could not stand at his work, he could hardly walk without becoming exhausted. At 19 he had severe headaches referred to the intratemporal region which persisted in spite of all measures. These headaches he described as "crushing." At the same time his hands enlarged while under our observa-

tion. The fatigability was so great that he would have to take to his bed and remain there. His past history was typical of the thymic. Nose bleeds, general weakness, enuresis, over-extensibility of the

FIG. 10

Fig. 10. W. W. Case 5. Six feet, 4½ inches. Fully compensated case. Great length of leg compared with length of thorax. Feminine waist; feminine pubic hair; acromegalic hands; no hair on face.

joints. His family history was a typically endocrine one. On his mother's side four members of direct and collateral branches had goitre, two with exoph-

thalmos. His father never shaved until the age of 28. Puberty in this patient was reached at 19. Hairy growth in the axilla and on the face remained absent. To this day he has never shaved. During the period of intense headaches and growth, he had various vagotonic symptoms: hyperacidity; excessive perspiration; precordial distress; nausea and vomiting; marked pallor; lack of libido. His gastric distress became so acute that operation was advised at another hospital for gastric ulcer. At this time an X-ray of the skull was taken and showed a large sella turcica, with practically no clinoids present at all and erosion at the edges. His photograph (fig. 10) has some interesting points. The extreme length of leg compared with thorax is noteworthy. The feminine distribution of pubic hair and feminine waist are present. His extremely large hands and generally deficient masculature attract notice. This photograph was taken about a year ago when he was just completing his cure. Today he has gained 30 pounds in weight and is feeling practically well, working constantly as machinist and supporting his family of wife and two children. During the last three years, his blood pressure had gradually risen to 130 mm. systolic from an initial 90 to 100 systolic; his gastric symptoms have abated, the white line of adrenal deficiency is disappearing; his fatigability has passed; libido has returned, and he is to all purposes cured of his malady. His fatigability and headaches in the past three years could always be improved with the administration of whole gland pituitary extract and gradually it became possible to diminish the dose and to allow the compensation to proceed unaided. He has now been with-

out treatment for practically six months. He seems to be a fully compensated case.

Discussion. The history and progress of this case is typical of all cases passing through the complete syndrome and is presented as a type of which I have now seen at least ten examples. It must not be forgotten that he now shows giantism plus acromegaly. That does not mean that his clinical picture indicates treatment. Far from it. He is a finished case. The giantism and acromegaly are incidents merely of the compensatory process—they themselves do not necessarily indicate present disease. This is a point well worth remembering. Many cases showing endocrinopathic features come under our notice and it should be our first aim to determine whether or not they represent processes that have come to a stop through compensatory efforts of which they are the indices. Under such conditions of course no treatment is called for. An interesting case of this nature was seen at Mt. Sinai Hospital, New York, in the service of Dr. Goldenberg, through the kindness of Dr. I. Strauss. A woman, 53 years of age, with typical acromegaly—hands, feet and skull abnormalities, was admitted for some minor ailment. Her history showed that she began to menstruate at 19 years, had intense headaches at 25 years which for three years resisted all attempts to alleviate, and during whose persistence she began to grow acromegalic. When the headaches spontaneously ceased, the abnormal growth ceased, and she passed an uneventful life to the time of the present slight ailment. Her childhood and adolescence were like those described in the first two stages of this syndrome—fatigability, being the prominent symptom. Her

acromegaly then, was completed at about the twenty-ninth year, did not further increase, and she remained well for twenty-three years longer. This was also a "finished" case as far as the syndrome of thymus, adrenal and pituitary was concerned. This case might be many times duplicated.

UNCOMPENSATED CASES

I desire to give rapidly the salient features only of several uncompensated cases belonging to the syndrome.

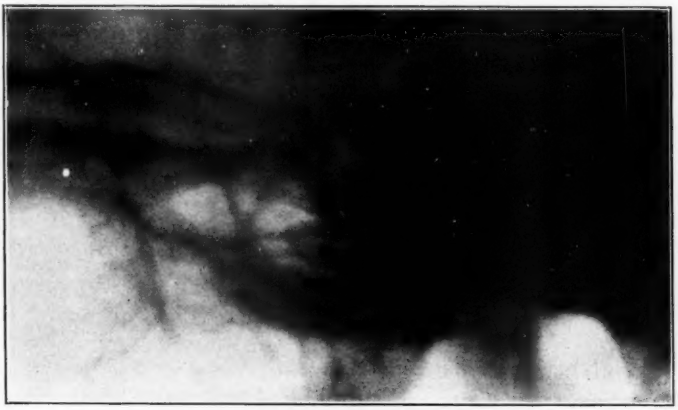

FIG. 11

Fig. 11. J. S. Uncompensated case 6. Shows pituitary fossa completely enclosed. Stereoscopic plates confirm this. Age 22 years; height 6 feet.

Case 6. Miss J. S. Referred by Dr. Robert T. Morris. Height 6 feet, large hands and feet, extreme fatigability, headaches, vagotonia, rapid growth in past two years with a past history of status thymico-lymphaticus; comes for relief of her headaches and fatigability. Blood pressure 95 systolic; blood sugar .065%; fatigue so great that she must remain prone the greater part of the day. In-

tense white line. Her sella turcica (fig. 11) shows a roofing in by the clinoids. Pituitary feeding gave gratifying results, but must be continuously carried out.

Case 7. T. R. Age 35 years; height 6 feet, 1 inch. Obese (220 lbs.). Early fatigability. Late puberty. Feminine pubic hair. Unmoral. Intense intratemporal headaches. Although wealthy, and of excellent family, commits sexual and other excesses. Frequently in jail. Fatigability and headaches per-

FIG. 12

Fig. 12. T. R. Uncompensated case 7. Age 35 years; height 6 feet, 1 inch. Sella turcica completely shut in and extremely small. Confirmed by stereoscopic plates.

sist. With beginning of headaches growth began. Blood pressure 95 mm. Sella turcica small and closed in by the clinoids (fig. 12); polyuria. Pituitary feeding helped not only his headaches and fatigability, but strangely and unexpectedly his moral sense is elevated and his excesses are no longer indulged in. But the pituitary feeding must be constantly kept up. A few weeks of discontinuance

leads rapidly to the old condition. He has been now practically free of his troubles for two years.

CONCLUSION

The syndrome of thymus--adrenal—pituitary combination is one frequently met with and its various stages are easy of recognition. The main characteristics of fatigability, low pressure, headache and growth are invariable components of the syndrome and depend upon mal-adjustments of endocrine interactivity. Stabilization of the balance may be spontaneously produced providing the sella turcica may be made to accommodate a hyperactive hyperplastic pituitary gland. This is done presumably by erosion of the bony capsule of the gland. In cases of inability of such enlargement of the sella, the syndrome persists, but the symptoms may be alleviated by the feeding of pituitary extract continuously. In the course of the syndrome other glands may be brought into the complex and alter the picture somewhat, but these are vagaries and seemingly have no great determining effect upon the course of events. Once recognized in any of the early stages, the further general progress of these cases can be prognosticated with a great degree of accuracy; and intervention, if necessary, can be undertaken with a large degree of success in the amelioration of the distressing symptoms.

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IS THERE A THYMIC HORMONE?

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From the frequency with which reference is made to the internal secretion of the thymus, and the various influences which this organ is commonly declared to exert over other parts of the body, it would seem superfluous to question the existence of a thymic hormone. But as a matter of fact, it has never been definitely proven that this organ produces any internal secretion at all.

For some time it has been the practice of workers in biology and medicine to declare that this or that organ or tissue of unknown function has an internal secretion, with little or no valid evidence to support their theories. Recent literature contains several "new ductless glands."

Morphologists having pointed out the fact that in the human species the thymus "usually" begins to undergo involution at "about" the time of puberty, experimentalists seized the fact and built upon this slender foundation various theories of control of sexual development by the thymus. Later it was pointed out that this correlation between the time of thymus involution and sexual differentiation does not exist generally among animals, but varies within wide limits, and also it was pointed out that in the human the thymus in many cases reaches its greatest size before puberty and in many other cases much later than puberty, but the theory had already been firmly established in the minds of many people, and it still persists. Below we shall point out

that the thymus is relatively larger at birth than ever after that time.

Another theory of thymic function arose from the fact that during the greater part of the involution of the thymus, the skeleton is growing rapidly. This theory stated that the thymus controls skeleton growth.

In regard to the theory of the thymus-skeleton relationship it may be pointed out that another lymphoid organ, the pharyngeal tonsil, "usually" begins its involution during infancy. If it so happened that some other striking phenomenon occurred at the same time, there would doubtless have arisen one or more theories on the inter-relationship of the two.

The fact that the thymus and thyreoid both have their anlagen in the pharynx gave rise to various theories of the relationship between these two organs.

Whenever in the life of an animal two phenomena occur together, and especially if they are not well understood, there has been a tendency to evolve theories associating the two functionally. Danchakoff ('18) in discussing another subject has well said, "The infinite complexity of developmental processes requires special caution in the attempt to establish a direct causality in the relations between two invariably concomitant phenomena." In no field of biology has such caution been disregarded more frequently than in endocrinology.

Most of the experiments with thymus can be placed under the headings, extirpation and administration of thymic tissue or extracts. In the lower animals there is relatively little lymphoid tissue other than the spleen and thymus and experiments

with the thymus in these forms should therefore be very instructive because of the relative simplicity of the problem. Removal of the thymus from frogs apparently is not fatal (Vincent, '04), but the animals seem less resistant to infections (Verenke, '99). Allen ('18) has recently shown that frogs will develop without the presence of the thymus. He removed the anlagen of this organ from young frog-larvae before it could possibly have functioned, and yet the larvae grew normally and metamorphosed at the normal time. Allen has not as yet, however, published any obervations on the effect the experiment may have had upon the spleen, but he showed conclusively that the thymus is quite unnecessary for the proper development of frogs. The same is probably true for other amphibia.

In feeding experiments with these forms, Gudernatsch ('14) found that thymus fed to larvae delayed their metamorphosis although the animals grew on this diet. Romeis ('15) and Abderhalden ('15) were able to verify these results in part, but Swingle recently ('16) states that such larvae kept by him on a diet of thymus were able to grow and metamorphose normally. Uhlenhuth ('17) feeding thymus to another amphibian (Amblystoma), obtained in general, negative results. This author believed that the delay in metamorphosis obtained by thymus feeding is due simply to the fact that thymus is not a sufficient food. He obtained delay in metamorphosis also by a diet of worms. The very numerous recent papers of Osborn and Mendel and others, show that many diets, although fed in abundance, lack certain constituents necessary for growth.

Metamorphosis in amphibia is probably initiated by skeletal changes which in turn depend upon the calcium metabolism. This metabolism is probably dependent upon the thyroid or hypophysis, or both, since removal of either of these two glands will delay if not entirely prevent metamorphosis. In this interference with metamorphosis which is caused by thyreoid removal (see Hoskins ('18), the thymus appears to be in no way affected, either in size or structure. Gudernatsch's results were obtained by feeding thymus-tissue from mammals, which of course have no need for a "metamorphosis-preventing" hormone, and hence are unlikely to have developed one.

In extirpation experiments with higher animals, the results are conflicting. Klose and Vogt ('10), Lucien and Parisot ('10), Paton ('11), Friedleben ('58), Matti ('12), Soli ('10), and other authors report that following thymus removal in birds and mammals various effects are produced, such as interference with skeletal growth, including rachitic changes, adiposity, emaciation, injury to the thyreoid, no effect on thyreoid, degeneration of testes, no effect on testes, etc. Pappenheimer ('14), Park ('17), and others, state that if the experiments are carefully performed and carefully controlled, the thymus can be removed without producing any harmful effects whatever. Paton and Goodall ('14) noted a decrease in the number of circulating leucocytes after thymus extirpation, and this seems to indicate that the thymus produces leucocytes as indeed is obvious from its microscopical appearance.

Hewer ('16) reports that injury to the thymus by X-ray irradiation results in injury to the function

of the testes. Since complete destruction (removal) of the thymus has no such effect and since unhealthy animals never breed well, Hewer must prove that her treatment did more than injure the health of her animals.

In feeding thymus to animals, Hewer ('14) claimed that the treatment injures the testes, a result not consistent with her report just mentioned. Hoskins ('16) feeding thymus to mammals obtained negative results on the growth of the body and all organs.

R. G. Hoskins ('10) states that feeding thyreoid causes hypertrophy of the thymus, but E. R. Hoskins ('16) obtained negative results with similar experiments.

Calzolari ('98), Henderson ('04), Hatai ('15), and others found that gonadectomy delays involution of the thymus and may even cause hypertrophy. There are also other changes produced by this operation, such as deposition of fat throughout the body, hypertrophy of the suprarenals and hypophysis in the male and decrease in the size of these two glands in the female. The changes that occur in the thymus may be secondary and not show a direct relationship between the thymus and gonads, especially since changes other than that of mere size may occur in organs other than those mentioned. The subject needs further investigation, particularly on the microscopical side. A possible cause of the delay in thymus involution after gonadectomy will be discussed below.

Clinically many functions and diseases are attributed to the thymus. Many of these theories are

based upon the concomitant phenomena already mentioned.

"Hyperactivity" of the thymus is frequently described where percussing indicates a dullness in the region of the sternum or a shadow is shown there by X-ray. This condition is described in cases of "mors thymica" and exophthalmic goitre. As a matter of fact it is questionable without an autopsy whether such enlargement of the thymus is not due simply to an unusually large deposit of fat. Often the size of the thymus is maintained in this manner, although relatively little thymic tissue is present. Moreover, the variability of the thymus is so great that the gland often persists normally until late in life, as is disclosed by autopsies of accident cases. Anatomists make an allowance of from one hundred to seven hundred per cent in the normal weight of the thymus at different ages.

Whenever in clinical cases there is an actual overgrowth of thymic tissue (or an early atrophy) this change may be brought about by the factors causing the disease in question, or still other and independent factors may be the cause, rather than that the thymus itself produces the clinical condition under consideration. We may be dealing with concomitant phenomena not directly related. In many cases where the disease is attributed to thymic changes, no autopsy is or can be performed, and the diagnostician does not really know whether or not the thymus is even pathological.

Hammar ('16), who has investigated scientifically the subject of "mors thymica," in a large number of cases, has found that the thymus is often

perfectly normal as compared with that seen in children killed by accident.

Melchior ('17) has pointed out the fact often disregarded, that although an "enlarged" thymus is frequently found in exophthalmic goitre, the symptoms are not different when the thymus is not enlarged.

In inanition and in wasting diseases, the thymus tends to atrophy. This fact is used in the theory of the relation of the thymus to general metabolism. Jackson ('15, '16), Stewart ('18), and others have recently investigated experimentally the subject of inanition. They find that in young starving animals there is a decrease in the size of the thymus, but the same is true of other organs and tissues. Certain tissues, especially the connective tissues, have a very strong growth tendency and where nourishment is insufficient in amount for all bodily needs these tissues grow or maintain themselves at the expense of other tissues and organs with a weaker growth tendency. Among these latter are included the thymus, thyreoid, heart, liver, spleen, alimentary canal (including the pancreas), lungs, and other soft parts. In older animals suffering from acute or chronic inanition, there is a marked loss in weight of the spleen, liver, and alimentary canal (including the pancreas), and a less extensive loss in weight of the kidneys, heart, lungs, hypophysis and testes. The thymus in these animals had already undergone "age involution," and hence was not affected. From these experiments it would appear that the loss suffered by the thymus in inanition does not indicate that this organ is affected differently from many other organs and does not

add any definite proof that the thymus has any control over metabolism.

Difficulty in breathing is often attributed to pressure by an "enlarged" thymus against the trachea and bronchi, but an anatomical study would show that these organs are the most unyielding structure within the thorax, and are separated from the thymus by a mass of yielding soft tissues in the mediastinum. It would also be very difficult for the thymus to exert sufficient pressure on the lungs to interfere with breathing on account of the fact that one ordinarily uses much less than the entire expansion of the lungs during respiration. Even with a considerable portion of the thoracic cavity filled with abnormal tissue there would still be left sufficient room for breathing.

The theory that rachitic changes in children are caused by the thymus cannot be proven by any known facts. The theory is based upon the fact already referred to that the skeleton and thymus grow at the same time; upon the changes in the skeleton thought to result from extirpation of the thymus; and upon changes thought to be noted in the thymus of rachitic children. The concomitant growth of the thymus and of the skeleton may not be causally related, the extirpation experiments have been lately discredited, and unless the children are suffering from inanition the thymus is as often normal as not. The faulty metabolism which causes the rachitic condition is sufficient in itself to explain the atrophy of the thymus.

There are theories of thymus function other than those noted above, which rest upon still weaker foundations. For example, Kaplan ('17) associ-

ates a certain dental condition with the thymus by the term "thymodontia." His theory is dependent upon the facts that children have thin teeth and a thymus. They also possess other organs such as tonsils, the pharyngeal, one of which normally begins to disappear in infancy. The dental condition Kaplan describes might as well be called "tonsildontia."

Pighini ('16) states that following vagotomy in chickens there results an atrophy of the thymus. There are also other changes including respiratory and circulatory difficulties which affect the metabolism and may in that way injure the thymus and other tissues easily affected by inanition. Furthermore, the question of thymic involution in chickens has never been adequately worked out.

Haneborg ('16) blames the thymus for chorea minor because this disease occurs between the ages of two and sixteen years, during which time the thymus is normally growing to its maximum size and because thymus administration seemed to be beneficial to his patients. He weakens his argument by the statement that there is much to sustain the assumption that an infection is the primary factor, perhaps an encephalitis. The latter condition alone might well account for the increased irritability of the nervous system in his cases.

"Hyperactivity" of the thymus is described even without determining whether the "enlargement" of the thymus is due to fat, to pathological tissue or to normal tissue. A disease of the thymus itself might cause enlargement of the organ and result in "hypoactivity" rather than "hyperactivity."

The evidence for the belief that the thymus does not produce an internal secretion is both anatomical

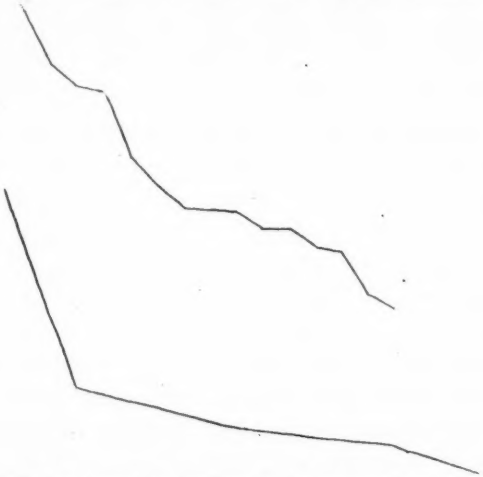
and experimental. Danchakoff ('16) has recently shown that the small thymic cells are truly lymphoid in character and that they arise from a polyvalent stem cell of mesenchymal origin, and also arise directly from the large thymic cells. This stem cell produces both lymphocytes and other leucocytes. Experimentally the small thymic cells can be changed into plasma cells and granular leucocytes.

Bell ('05) has shown that the Hassl's corpuscles arise from connective tissue. They are not present in all mammals nor in animals in general. They are not corpuscular as they appear in microscopical sections, but are strands which branch and ramify through the thymus as does other connective tissue. Hewer ('16) has produced them experimentally by injury to the thymus by X-ray irradiation. Similar structures are found in other lymphoid tissue in certain pathological conditions, especially around the parotid gland.

It may be pointed out that with our newer technical methods, it is possible to demonstrate microscopically secretory activity in all organs known definitely to produce a secretion, and in the thymus such activity cannot be demonstrated. The cells which make up thymic tissue belong to the vascular system and their function is no more likely to be the formation of an internal secretion than cells of similar appearance in other lymphoid tissues. If the thymus is a ductless gland then this must probably be true of the tonsils, lymph nodes, spleen, Peyer's patches, and very numerous small aggregations of lymphoid tissue scattered throughout the body. No one would probably be willing to include

all these organs in endocrinology. The involution of the thymus no more indicates a secretory function than does that of the pharyngeal tonsil already referred to, "hyperactivity" of which, as indicated by its hyperplasia, is ordinarily called simply adenoids as is doubtless proper.

The following graph and table prepared from data furnished by Rabinowitsch ('13), Donaldson ('95), and Hammar ('06), shows clearly the temporal relation between the involution of the thymus



The upper line shows the decrease in the percentage of lymphocytes in the blood, from 61 per cent at one year to 23 per cent at puberty (14.8) years. The lower line shows the concomitant decrease in the size of the thymus (amount of thymic parenchyma) from 0.0385 per cent of body weight at birth to 0.0020 per cent at 18.2 years of age.

and the decrease in the percentage of lymphocytes in the blood; and the relation of the size of the thymus to that of the body. During the period of infancy and childhood there is also a loss of lymphoid tissue other than the thymus, including the pharyngeal tonsil and other masses all over the body. In very old people lymphoid tissue is very scant.

The graph shows a marked parallelism between the decrease in the percentage of lymphocytes in the blood and the decrease in the relative amount of thymic parenchyma between birth and puberty.

Age years aver.	Body weight Kg. aver.	Thymus weight gms. aver.	Thymic parenchyma wt. gms. aver.	Thymus per cent parenchyma aver.	Thymus per cent body wt. aver.	Thymic parenchyma per cent body wt. aver.	Lymphocytes in blood per cent aver.
Birth	3.2	13.3	12.33	93.	.0401	.0385	61.0*
2.6	14.2	23.	19.26	84.2	.0162	.0136	55.5
9.	27.4	26.1	22.08	84.6	.0090	.0080	36.0
14.8	45.5	37.5	25.18	67.1	.0082	.0055	25.0
18.2	62.2	25.6	12.71	49.7	.0041	.0020	23.0
23.3	67.	24.7	4.95	20.0	.0037	.0007	23.0

*Percentage at 1 year, higher at birth. Leucocytes at birth equal 18,000 to 36,000 per cu. mm.

The accompanying table shows that although the thymus reaches its greatest absolute size at about the time of puberty, nevertheless, in relation to the size of the body for all of which it functions, it is seven times as large at birth as at puberty, changing thus from 0.0385 per cent of the body weight at birth to 0.0055 per cent at 14.8 years of age. The table also shows that in the growth of the thymus after birth the connective tissues make up an increasing amount of the entire organ. The amount of connective tissue and fat in the thymus changes from 7 per cent of the organ at birth to 32.9 per cent at puberty and 80 per cent at twenty-three years of age. In old age the non-lymphoid part becomes nearly 100 per cent of the thymus. Again in the absolute amount of parenchyma of this organ it nearly reaches its maximum size at nine years of age when there is present 22.08 grams of lymphoid tissue as opposed to 25.18 grams at puberty. This increase in the amount of lymphoid tissue is relatively much less than the relative in-

crease of the entire body. These figures are of course averages.

In consideration of the theory of the influence of skeletal growth by the thymus, it should be noted in the table that during the period between 14.8 and 18.2 years of age when the skeleton is growing very rapidly the actual amount of thymic tissue decreases nearly one-half, from 25.18 grams to 12.71 grams, and the relative amount nearly two-thirds, or from 0.0055 per cent of the body weight to 0.0020 per cent. The skeleton also grows rapidly before puberty and while the thymus is still large. The inference here is inevitable that the thymus does not control the growth of the skeleton, as is so often claimed.

In its evolution the thymus resembles the tonsils of higher forms. In primitive life (as illustrated by fishes and by young mammalian embryos) the thymus was intimately associated with the gill pouches of the pharynx in much the same relation as that between the pharynx and tonsils of the highest animals today. In the change from aquatic to terrestrial existence the gill pouches, as such, disappeared and the pharyngeal wall was thus pulled medially and separated from the thymus which then lay in the neck as it does now in intermediate forms. With the skeletal changes that occurred in mammals and the shifting caudally of the cervical and thoracic viscera, especially the heart and its great vessels, the thymus was pulled into the thorax, where it now lies in the higher animals. This change of the position of the thymus can be followed in comparative anatomy and in mammalian embryology. One might even theorize that

the thymus is a misplaced tonsil in the higher forms and atrophies finally because it cannot function as a tonsil on account of its separation from the pharynx. Its persistence in the lower forms where it remains in relation with the pharynx would support such a theory. This view would also find support in the fact that in frog larvae where metamorphosis is prevented by removal of the thyreoid, the thymus remains in close relation with the pharynx and persists, becoming enlarged with the excessive growth which these thyreoidless animals undergo.

A more logical theory of the significance of the thymus is that it functions as a lymphoid organ in infancy and childhood when large numbers of lymphoid cells and leucocytes are needed to combat infections. The large number of leucocytes and especially lymphocytes in the blood during this period of life indicates that these cells are relatively very important to the organism. The question of the relative loss of thymic tissue and other lymphoid tissue all over the body that begins at birth and progresses throughout life, especially in infancy and childhood, must be bound up with the question of the development of immunity from, or resistance to, infections that occurs in every animal. It is a fundamental law of biology that bodily structures the need for which decreases, tend themselves to atrophy.

The loss of vitality that occurs after castration suggests the need of the retention of the thymus and other leucocyte producing tissues as actually occurs.

It is idle to discuss the enlargement of the thymus and other lymphoid tissues in status lymphat-

icus until something more has been learned about this condition which is as yet not understood.

The belief in the lymphoid nature of the thymus is by no means new. Adami and McCrae ('14), in their excellent work on pathology, state on page 563, "To all intents and purposes it (the thymus) is a lymphoid organ." Many others have held the same view.

Whatever be the real function of the thymus, certain it is that its production of an internal secretion has not been proven. The evidence in favor of such a theory is but circumstantial at best and very meagre. It is equally difficult to prove that the thymus does not produce a secretion, but the burden of proof is upon those who support the former theory. A statement is not true because it cannot be proven untrue.

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ACTIVE COOPERATION BETWEEN THE PHYSIOLOGIST AND THE CLINICIAN AND COMPARATIVE ANALYSIS OF COORDINATED DATA IN THE STUDY OF THE INTERNAL SECRETIONS*

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The purpose of our Association being the study of the internal secretions, you will surely realize that it would give me great pleasure to initiate this, our first scientific meeting, with at least an outline of the great progress accomplished in recent years. Unfortunately, my remarks will rather tend in the opposite direction, although my purpose, I hasten to state, is to suggest ways and means that may enable us to hope at least, for a better outlook.

It happens to have been my lot, in addition to active practice, to edit works which aimed to collate, either in logical sequence, or in encyclopedic form, the progress recorded in the medical literature. This class of work, which has taken up much of my time and labor during the last thirty years, involved a review of all the branches of medicine, including the specialties, fifteen times. From its very start, in 1887, I became impressed with the thought that closer cooperation between the clinician and the physiologist would tend greatly to elucidate our knowledge of disease. Each of the nine series of my Annual of the Universal Medical Sciences will, in fact, be found to contain admirable reviews of the contributions to physiology during the corresponding years, by Prof.

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H. Newell Martin, of Johns Hopkins, up to 1890, and by Prof. W. H. Howell, his successor, up to 1896. Unfortunately, the panic of the early nineties, by undermining the resources of the work, imposed the elimination of the department of physiology, with others devoted to auxiliary subjects, from its successor, the Analytical Cyclopedia of Practical Medicine. This is mentioned only to illustrate the importance I have always attached to the active cooperation I urge. Indeed, to us, clinicians, who are responsible for the multitude of lives entrusted to our care, physiological data are as many precious additions to those garnered at the bedside, in the pathological laboratory and through our therapeutic results, for the elucidation of the complicated problems that are constantly surging up before us. For, after all, what is the condition we term "disease," however caused, but "pathological physiology," as Bouchard has well termed it?

Indeed, so close is his connection with physiological problems in his daily contact with disease that the physician sometimes discovers a solution. Thus, a great physiologist, Professor Pawlow, of Petrograd, wrote sixteen years ago (1), after referring to the discovery of gastric secretory nerves: "Physiologists, on the other hand, had fruitlessly endeavored for decades to arrive at definite results upon this question. This is a striking, but by no means isolated, instance where the physician gives a more certain verdict concerning physiological processes than the physiologist himself; nor is it indeed strange. The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never

make their appearance in the normal course of life. It is a series of physiological experiments which Nature and life institute, often with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at our command. Clinical observation will consequently always remain a rich mine of physiological facts."

The broad field of endocrinology is in a great measure based on clinical findings, and time may show that the very obscurity which surrounds the whole subject at the present time, is due to the fact that we have too freely ignored the inspirations, in conjunction with physiological discoveries, of the morbid processes that Addison, Graves, Marie, Launois, Frölich and others have described. I shall illustrate later in the course of my remarks, by a few examples among the many available, the elucidative value of clinical data in physiological questions. It will serve to emphasize anew the material advantage that would accrue from closer cooperation between the physiologist and clinician than now prevails—an opportunity greatly facilitated by our Association and particularly through its organ, Endocrinology.

The ways and means favoring such a cooperation being thus available, how should we use physiological and clinical data in our search for truth? Again, time being an important element, in view of the growing recognition by many clinicians of the first order of an unmistakable influence by certain of these organs on various fatal diseases, including some encountered during the present war, how could we hasten progress?

As an example submitted below will show, comparative analysis of coordinated data, i.e., garnering of all available data on a given subject, then arranging these data in logical order and sequence, will not only meet the first requirement, but point to the labors required to complete the work necessary to attain a satisfactory conclusion concerning the identity of a function. Various theories may be suggested by the coordinated data when carefully tabulated; a sound working hypothesis will soon assert itself by the wealth of facts from various directions for which it will afford a ready nidus, while wrong theories will soon meet their doom through lack of corroborative testimony, direct and indirect, and through its inability to find a logical place anywhere.

Purely to illustrate the workings of such a plan—which I have now followed myself, as far as private means could permit, for many years—I will submit a brief review of the present status of the prevailing views concerning the functions of the adrenals, and compare it with the totally different aspect of the question which the plan advocated offers.

In the April, 1917, number of "Endocrinology," you doubtless read the original article written by our fellow member, Prof. Swale Vincent, of Winnepeg, on recent views as to the functions of the adrenal bodies. Among the features reviewed is the discovery of Oliver and Schaefer in the early nineties, to the effect that "the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-pressure and to sustain the tone of the tissues innervated by the sympathetic system." You will also recall the experimental data which he adduces to show that Schaefer's view is no longer ten-

able. Those of Young and Lehmann are quoted to show that ligation of the adrenal veins during thirty minutes, to dam back the adrenal secretion into the organs, and then allowing, on release of the ligature, the accumulated secretion to flow into the circulation, failed to evoke the expected result. Very little if any fall of blood-pressure followed ligation of the adrenal veins. "In fact," writes Vincent, "the experiments merely show that adrenin is poured out into the adrenal veins." Similar experiments carried out by Young, but with the adrenal veins tied several hours to exclude the adrenals totally from the circulation, gave similar results, there being no appreciable fall of pressure. Even removal of the adrenals by Austmann and Halliday, with concomitant observation of the blood-pressure, until the animal died, failed to affect the pressure curve more than would have ether administered as long as possible. The older experiments of Moore and Purinton, and the more recent observations of Hoskins and McClure—to which many others might be added—are quoted to show that inasmuch as very small doses of adrenin will lower the blood-pressure, the amount of adrenal secretion poured out into the adrenal veins would tend to keep the blood-pressure down rather than up. Briefly, the one great function upon which the practitioner has depended twenty-six years, the blood-pressure theory, should now be abandoned.

Virtually the same conclusion is reached concerning the second theory which has attracted some attention, the so-called antitoxic theory of Abelous and Langlois, in virtue of which the toxic effects of certain substances are neutralized by a substance elaborated by the adrenals. While referring to a few

isolated records which seem to favor it, Vincent states that "it must be confessed that the antitoxic theory has not been substantiated." On the whole, a few minor suggestions concerning possible functions, including the emotional stress theory of Cannon and de la Paz, and a summary of what he deems to be the state of our knowledge concerning the adrenal bodies, seem fully to substantiate Vincent's remarks early in the article that "we know nothing of the functions of the adrenal body regarded as an organ on its own account."

And the adrenals are not alone in this plight. The functions of the thyroid, parathyroids, thymus, pituitary, pineal and other organs of the series, are likewise well known to be obscure. One and all, viewed from the standpoint of prevailing teachings, stand in the light of another of Vincent's remarks concerning the adrenals: "There is no good evidence of an experimental or clinical nature which warrants us in believing that the adrenal body as a whole has any definite function."

Need we wonder under these circumstances that so erudite and conscientious a surgeon as Prof. W. S. Halsted, of Johns Hopkins, should be driven to write three years ago, after an attempt to elucidate the frequently fatal form of Graves's disease in which the thymus complicates the morbid process: "It must be evident to everyone that there reigns the greatest confusion on the subject of the functions of the glands of internal secretions"?

Gentlemen, it is difficult to conceive how all the work done since Oliver and Schaefer published their first paper on the influence of adrenal extracts on the blood-pressure, twenty-four years ago—or indeed.

since Brown-Séquard published his initial dissertation on the adrenals over sixty years ago—can thus have proven futile. My own belief is that such is not the case. Comparative analysis of coordinated physiological and clinical data tend not only to sustain this opinion, but also to suggest that the adrenals *may* carry on a function of major importance—a function, moreover, capable of accounting for and including, as fragmental expressions of that function, what roles both physiologists and clinicians have attributed to the organ and sustained by considerable evidence.

The main features which led me to submit what might be termed the "respiration theory" fifteen years ago, and which much of the evidence recorded herein, has sustained since then, may be said to have rested upon five main conditions: (1) Addison's disease; (2) adrenal lesions in acute diseases; (3) certain adrenal tumors, such as hypernephroma; (4) large adrenal grafts; (5) the unsettled state of physiological knowledge concerning respiration and metabolism.

As to Addison's disease, the older contention that the adrenals were not always diseased, and that we were therefore dealing with a neurosis, is no longer tenable. Inasmuch as the disease has been shown to affect any part of the chromaffine system, including its ganglia, it is to disorders of that system that we must attribute the Addisonian syndrome, the leading or salient symptoms of which are progressive asthenia, weak heart action, vascular hypotension, emaciation, hypothermia, dyspnoea, vomiting, diarrhea, and, only in cases of sufficient duration, bronzing.

In the course of certain infections, diphtheria, scarlatina, malignant endocarditis, typhoid fever, pneumonia, etc., and particularly towards the close of these diseases, symptoms are observed which correspond with those of Addison's disease, viz., extreme asthenia, low blood-pressure, hypothermia, rapid breathing, cyanosis, weak pulse, tendency to syncope and heart failure. The post-mortem adrenal lesions in such cases vary from marked reduction of the residual adrenin and disappearance of chromaffin reaction, with cellular atrophy, to more or less marked interstitial hemorrhages, attaining in some cases the degree of adrenal apoplexy with sudden death. Among the recently described cases of this class may be mentioned those of Josué (2), Goormaghtigh (3), and Moltschanow (4). Excessive exertion in soldiers suffering from malaria, as often noted during the present war by Paisseau and Lemaire (5), or dysentery, as observed by Remlinger and Dumas (6) and Steiger (7), may also bring about adrenal lesions and in some instances adrenal apoplexy. Burns, according to Kolisko (8), may likewise produce this form of hypoadrenia. As I have been able personally to verify, 8 to 12 minim doses of adrenalin given hypodermically, in small quantities of saline solution, are positively life-saving in uncomplicated toxemias.

Hypernephroma, a form of tumor shown by Grawitz, in 1883, to develop from adrenal tissue, either in the adrenals themselves or in the kidneys, vascular walls and other tissues, may be composed of either or both cortical and chromaffin substance, though often merged with other neoplasms, cysts, papilloma, etc. When it occurs between the first and eighth year, as is often the case in the true adrenal

type, it may give rise to abnormally rapid body growth. In a case reported by Owen Richards (9) in a girl of seven years, the development was that of a woman of twenty. Such cases may show marked muscular development and strength. Parhon and and Golstein (10) refer to a boy who, between the ages of 9 and 14, attained the size of a "vigorous man." Jump, Beates, Jr., and Wayne Babcock (11) refer to a case of theirs in a girl of seven years, as "remarkably strong." This overdevelopment, however, shows none of the characteristics of acromegaly. Common to this type also is premature sexual development with profuse hirsuties, swarthy skin, etc. There is, as a rule, excessive appetite and thirst; gastric disorders and stubborn vomiting are sometimes observed.

The fourth feature was suggested by the fatal effects of large adrenal grafts. Bra (12), after grafting the adrenals of a dog into the cellular tissue of a child, witnessed its death in three days. Jaboulay (13) lost two cases, within twenty-four hours, after the same procedure. Courmont (14), in reporting a fourth case which likewise died in twenty-four hours, refers to the presence of "a formidable hyperthermia and cardiac collapse" while specifying that there was no infection of the wound. Nor had any been observed in the previously reported cases.

If any clue could be obtained from these clinical conditions as regards the function of the adrenal bodies—or rather of the whole chromaffine system in the light of modern work—it seemed to be that they at least played some important role in (1) metabolism, as shown by their influence on nutrition and general development and (2) on respiration, as shown

by their influence on oxygenation and the respiratory mechanism.

This brings in the fifth and last feature: the unsettled state in physiological literature of the very questions in point.

Concerning respiration, the many facts recorded by physiologists of the rank of Bohr (15), Haldane and Lorrain Smith (16), Vaughan Harley (17), Henriques and others, have tended to show that the diffusion doctrine of respiration is not valid. Pembrey (18), after an impartial study of the question has expressed the view that "the body of evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." What is meant here by "secretory theory" is that, as expressed by Bohr and Henriques (19), the respiratory process, to account for experimental facts observed, requires, in the lungs, a substance "having greater avidity for oxygen than the blood itself," or as they define it, "a kind of internal secretion." It is this function which from my own viewpoint the adrenal secretion seemed to fulfill.

We shall see later, that this view, which I submitted in 1903 and 1907 and repeatedly since in numerous articles, urging its importance in the intelligent interpretation of many diseased states, has recently (1917) been sustained by the researches of a physiologist, M. L. Menten (20), of the University of Chicago, who writes in this connection: "The presence of adrenalin in the venous blood of the capillaries of the lungs undoubtedly induces changes which meet the conditions suggested by Bohr (21) as requisite for an alternative to the explanation of oxygen secretion, that is, adrenalin could act as a substance

altering the property of hemoglobin so as to give it a greater attraction for oxygen as it passes through the lung."

COORDINATED DATA IN SUPPORT OF THE RESPIRATION THEORY*

These, reduced to their simplest expression, may be divided into six fundamental functional links:

1. *The adrenal secretion passes out by the adrenal veins then enters the inferior vena cava.*

As to the formation of the secretion, Stoerk and Haberer (22) found that the chromaffine substance develops in the form of intracellular granules which, when sufficiently dense, diffuse out of the cells into the adjoining small vessels and appear in the adrenal venules as a yellowish brown, refractile, mucoid material which constitutes the secretion that passes to the adrenal veins. According to Elliott (23), the adrenals of a normal man should contain from 4 to 5 mgm. (1/15 to 1/12 grain) of adrenin, but fright, anesthesia, infectious diseases and cardiac failure and post-mortem changes may reduce considerably this amount.

The presence of the adrenal secretion in the blood of the adrenal veins is suggested by the following facts: Gottschau (24) traced hyaline granules (found subsequently to be their secretion) from the interior of the adrenals to their veins. This observation was confirmed and amplified by Manasse (25), Aulde (26), and Stilling (27). Pfaundler (28) traced the same granules from the interior of the organ along the adrenal veins to the vena cava itself.

*The name "respiration theory" has seemed to the writer better to denote the process described—pulmonary and cellular—than the "secretory theory," which has no specific meaning, or "oxidation theory," which implies destruction by oxidation of the adrenal product and renders unnecessary the study of any function, since a "destroyed" substance cannot logically be credited with a function.

It is doubtless the adrenal secretion which is carried by the blood of the vena cava, for when blood originating from the adrenals on its way to this great trunk was injected into animals by Cybulski and Scymonowicz (29), it produced the characteristic effects of adrenal extract. These results were confirmed by Biedl (30), Langlois (31), and Dreyer (32), Szymonowicz, Biedl, Dreyer, Salvioli, and Pizzolini (33) found, moreover, that such effects could not be obtained with venous blood obtained from other parts of the body.

2. *The adrenal secretion inevitably reaches the pulmonary alveoli where a reducing secretion is required to account satisfactorily for the absorption of oxygen from the air.*

That the blood of the inferior vena cava containing the adrenal secretion reaches the pulmonary alveoli by way of the right heart needs but to be recalled.

We have seen that the classic diffusion doctrine of respiration has been challenged by a number of prominent physiologists, beginning with Bohr in 1897, and that this investigator and Henriques had concluded that a kind of "internal secretion" . . . . "having greater avidity for oxygen than the blood itself" was necessary to explain the phenomena witnessed. Besides their own observations based mainly on aerotonometric studies may be mentioned those of Paul Bert (34), who showed experimentally that the absorption of oxygen by the pulmonary blood persisted even when the pressure of this gas was almost *nil;* of Müller, who found that a strangulated animal exhausted the air in its lungs of all its oxygen; of Setschenow and Holmgren (35), Zuntz (36) and

others, who found but traces of oxygen in the arterial blood of asphyxiated animals.

3. *The adrenal secretion has affinity for oxygen, reaches the pulmonary alveoli and affects the oxygen exchange.*

Vulpian (37) found that adrenal juice reduced iron perchloride and iodine. Cybulski (38) recorded a similar action on potassium permanganate. Langlois (39) noted that adrenal extract lost its reducing properties *in vitro* when oxidizing compounds were added. Battelli (40) found that adrenalin did not lose its properties when contact with air was prevented, while Abel (41), Takamine (42), and others deem this property a source of trouble in laboratories, the latter chemist specifying that adrenalin becomes oxidized by contact with the air. A. L. Menten (43), a physiologist, adduces experiments which enable her to conclude that adrenin "does particularly affect the oxygen exchange in that organ"—the lung.

4. *The adrenal secretion influences actively the respiratory phenomena, including the intake of O and the output of CO_2.*

D. E. Jackson (44) found that adrenalin produced prompt dilatation of the bronchioles when these are contracted, wholly independently of any rise of blood-pressure. The immediate relief afforded by injections of adrenalin in asthmatic paroxysms, a treatment now resorted to in preference to any other, is probably due to this fact. Januschke and Pollak (45) noted that injections of adrenin in doses of 1/10 mg. (1/600 grain) caused an increase of the respiratory excursions of the lungs. Though noticeable in normal individuals it was especially marked in animals suffering from muscarin asthma. Nice,

Rock and Courtright (46) found that whether adrenin were injected in minute doses, causing a fall of blood-pressure or in large doses causing a rise of blood-pressure, it evoked an increase in the depth of the respiration. Byelaventz (47) found experimentally that adrenin increased the gaseous interchanges. Bernstein and Faltz (48) observed that injections of adrenin in doses of 1 mg. (1/60 grain) subcutaneously, in normal individuals produced an increased consumption of oxygen and, conversely, an increased excretion of carbonic acid. The respiratory quotient was likewise increased.

5. *The adrenal secretion influences tissue oxidation.*

Adrenal extracts, as first shown by Oliver and Schaefer (49), cause a rise of temperature when injected subcutaneously in doses of 8.57 Grams of fresh gland, made into an aqueous extract, per kilogram of dog. Reichert (50) also recorded a rise of 1°C. in dogs, accompanied by increased metabolism from adrenalin in doses of 0.001 Gm. per kilo of body-weight. Morel (51) observed a rise of 0.9 to 1.8 F. (0.5 to 1.°C.) in guinea pigs after rather large doses injected subcutaneously. Lépine (52) states that the increase of blood-pressure caused by adrenal extract in therapeutic doses is always followed by a rise of temperature. These observations seem controlled by the familiar facts that removal of the adrenals is followed by a steady decline of the temperature until death ensues.

6. *The adrenal secretion takes part in tissue oxidation and metabolism, by becoming a constituent of the hemoglobin.*

That the adrenal secretion can endow hemoglobin with its oxygen-carrying power, i.e., convert it into oxyhemoglobin, as I have repeatedly urged, has been confirmed by the observations of Menten and Crile (53), who noticed that the blood from the adrenal vein invariably assumed a bright red arterial color in from one to twenty minutes after dilution with salt solution, while blood from other organs treated in the same manner showed no change. This was found spectroscopically to be due to an increased formation of oxyhemoglobin. Menten (54) having added adrenalin to diluted human venous blood, found moreover, that it caused an increase in the intensity of the oxyhemoglobin absorption-bands (of which she gives photographs) and remarks that similarity between the spectra of adrenal vein blood and those obtained from venous blood to which adrenalin was added "is unquestionably very strong evidence that it is adrenalin which is responsible for the increased amount of oxyhemoglobin found in the adrenal vein blood."

RELATION TO OTHER THEORIES

The foregoing data, selected from labors of observers of recognized ability and standing, seem to suggest that the main disorders we, clinicians, attribute directly to the adrenals—the whole chromaffine system—are due, in so far as their symptomatic phenomena are concerned, to disturbances of that phase of metalobism and its corollary, nutrition, influenced by that system. Recalling the five clinical features which led up to this analysis, it would seem that Addison's disease and adrenal insufficiency due to infections may on good ground be attributed to deficient tissue oxidation, while typical adrenal hypernephro-

mata and large adrenal grafts produce their morbid effects through excessive oxidation.

True, various observers have not noted an appreciable alteration of protein metabolism in Addison's disease, but they lose sight of the clinical fact that the anorexia and inadequate assimilation of proteins may account for this. If, as observed by Senator (55) and others, the diet of these cases is increased and properly balanced, there is a notable gain. Particularly is this true if, as I have urged, adrenal gland or adrenalin is administered in *judicious* doses, i.e., doses adjusted to the blood-pressure and hypothermia, simultaneously. This coincides with the observation of Addis, Barnett and Shevky (56) that adrenalin administered subcutaneously in rabbits increases the urea excretion, provided the doses are not too small or too large. In the latter case, (as I have frequently observed in various nutritional disorders treated with adrenalin) cellular metabolism is interfered with by the undue constriction of the arterioles produced by the adrenal principle, and the resulting deficiency of arterial blood supplied to the cellular elements. Emaciation may thus be caused by its prolonged use by cases in which the disease present does not include emaciation in its pathology, bronchial asthma for instance. In one case, observed in consultation, the loss of weight exceeded thirty pounds. On the whole, there can be no doubt that the adrenal secretion influences metabolism.

This apparently applies likewise to the influence of adrenal products on the *blood-pressure*. There is no doubt that therapeutic doses raise the blood-pressure and that, as illustrated farther on in this paper, its continued use may induce a more or less perma-

nent rise of 50 mm. Hg. The clinic, therefore, supports the discovery of Oliver and Schaefer that adrenal extracts raise the blood-pressure. An increase of the rate of metabolism such as that induced by the adrenal principle also affects both smooth and skeletal muscles as also first observed by Oliver and Schaefer.

The *antitoxic function* attributed to the adrenals by Abelous and Langlois and others finds support in the fact that catabolism, that phase of metabolism in which tissue wastes, including the intermediate toxic wastes, are broken down, is partly due to oxidation. The conversion of these toxic wastes into eliminable end-products would then depend in a measure upon the integrity of the adrenals. Many clinical facts tend to sustain this view.

Finally, while the *adrenal cortex,* as much clinical evidence has shown, markedly influences both the sex characters and the premature development of sexual organs, hirsuties, etc., exaggerated oxidation, in which the organ *in toto* may take part, partly accounts for this morbid process, probably as a corollary to the specific role played by the cortex in the latter.

It would thus seem as if the adrenals through their dual action, specific and general, on metabolic activity were able to account for and explain the various "functions" that have been attributed to them. They all become, in the light of the foregoing, however, but fragmental expressions of a general function, thus justifying their authors for their deductions, though restricting them to their proper precincts.

VULNERABLE POINTS OF THE RESPIRATION THEORY

It is purely as a clinician—and one indeed, always ready to accept gratefully any degree of enlightenment—that I submit the following analysis of the weak points of the respiration theory that might be urged against it.

The minute quantity of circulating adrenin fails to meet the needs of the respiration theory. Analysis of this question, if current teachings are taken as standard, suggests that the minimum concentrations given are not based on a sound foundation. Thus, according to Trendelenberg (57), this concentration is one part in one or two billions in the carotid blood of normal rabbits. Yet, we are taught by physiologists that adrenin is destroyed in arterial blood.

Again, we are told that it is by oxidation that adrenin is destroyed, while as we have seen, Abel, Takamine and others, found this property a source of trouble in laboratories. And yet no precaution seems discernible in the various procedures recited by the different authors who assayed blood to determine adrenin concentrations. Under these conditions it is very likely that at least a part of the adrenin is oxidized in the course of these procedures. Even the figures given for the adrenal veins are open to suspicion since, as shown by Menten (58), dilution of their blood caused an increase of oxyhemoglobin, which would entail a decrease of adrenin.

When the destructive effect of oxygen on adrenin is taken into account it seems also that there should be but one vascular area capable of affording a reliable assay, viz., the venous field comprising the adrenal veins, the vena cava, the right heart and pulmonary veins up to the air cells, where the blood be-

comes arterial. Once at the air cells, the adrenal product should be destroyed and remain so throughout all arterial channels and the whole venous tree (unless resupplied, so to say, in the subsidiary adrenal tissues) until the adrenals *per se* are again reached. The concentration in the adrenal veins is 1 part in one million, according to several investigators quoted by Barger (59). The venous channels between these veins and the air-cells being, of course, much larger, it is probable that Battelli's concentration 1 part to 10 or 20 millions (60) is the correct one for caval blood i.e., one thousand times greater than Trendelenberg's.

On the whole, the actual minuteness of circulating adrenin in arterial blood cannot justly be cited to controvert the many concordant data submitted in favor of the respiration theory.

The great quantity of adrenin needed to produce the effects recorded would kill by paralyzing the alimentary canal. The invalidity of this objection is emphasized by the teaching of physiologists that "adrenin circulating in the blood is rapidly destroyed" by oxidation. Such being the case the adrenal secretion would meet its doom on reaching the alveoli, thus preventing any action either on the stomach or intestines.

Abundant clinical experience also shows that such an action is not produced either when adrenalin or the adrenal gland are given by the mouth or adrenalin is injected hypodermically, endomuscularly or rectally during short or prolonged periods in therapeutic doses. This applies also to children. I could produce a large number of cases in which 3 to 7 minims given orally several weeks served only to act as tonic, and

to increase the appetite. In keeping with the observations of Loeper and Verpy (61), it often promoted the secretion of HCl where hypochlorydria existed. A medical patient suffering from asthma wrote recently, requesting my opinion concerning the continued use of adrenalin: "I have employed it for *several months* once a day, sometimes twice a day, hypodermically in doses of 10 minims of the 1-1000 solution." His blood pressure rose from 130 to 180, he lost flesh and feared a permanent rise. Not a gastric symptom occurs, however, in the history of this case.

If inhibition of the rhythmic contractions of the intestine occurs in the lower animals, as shown by Ott, Magnus and others, even when injected in very low concentrations (1 to 20 millions, Magnus) (62), no appreciable effect of this sort is observable when adrenin is given in the therapeutic doses used in man. Possibly it occurs as an ephemeral effect of the constriction of the arterioles of the intestines similar to that caused by adrenalin throughout the body.

INVESTIGATIONS NEEDED TO DETERMINE THE VALIDITY OF THE OXIDATION THEORY

Some physiologists hold that the adrenals "in some way influence the metabolism of contractile tissues." If the word "metabolism" is actually meant here, it would seem as if the word "destruction" (of the adrenal secretion in the blood) should be replaced by its *conversion* into something else that is not subject to destruction by oxidation. I have long held that it entered the hemoglobin, and endowed it with its power to become oxyhemoglobin; we have seen that Menten found that the adrenal product actually becomes converted into that body.

If then it does become converted into oxyhemoglobin, the adrenal secretion or principle must be taken up by the red corpuscles. Mulon (63) has found that the latter gave some of the reactions of adrenalin. Again, Traube, in 1853, concluded that hemoglobin could not fulfill the functions attributed to it without the aid of a catalyst, a substance capable of hoarding oxygen and crowding it, as it were, on the tissues as an "accelerator." Poehl (64) found that the adrenal principle was a catalyst, while Jolles (65) pointed out that the activity of a given volume of blood as a catalyst corresponded with the number of red corpuscles it contained. This suggests that the adrenal secretion (not necessarily adrenin, which does not represent the secretion *in toto*) is the corpuscular catalyst which supplies the tissues with oxygen.

In this connection, and possibly accounting for the small proportion of secretion produced excepting under stress, such as fright, excitement (Cannon), hard labor, disease, etc., its active principle may be an oxidizing enzyme—"adrenoxidase," as I once termed it. As Bayliss (66) states, "enzymes are merely a particular class of catalysts, considered for convenience apart, owing to the fact that they are produced by living organisms and are for the most part *of unknown chemical composition.*" As an enzyme, adrenoxidase could act as an oxidizing catalyst without itself being destroyed. Now the oxidizing ferment of Bunge and Schmiedeberg (67), Jaquet (68), Abelous and Biarnés (69) and adrenin give heat reactions very similar to those of adrenin; while Menten (70) also refers to the influence of temperature on the activities of adrenin within fixed limits, a peculiarity of enzymes.

The adrenals or other chromaffine tissues would thus only be required to replace actual losses of the enzyme, the residual body asset of which would be conserved as the oxygen carrier and accelerator of the hemoglobin and constantly be re-used, while having lost its identity as adrenin. This would afford a legitimate nidus for the "function" suggested by MacMunn (71), who, having found haemochromogen in the adrenals, concluded that these organs served to break down worn out hemoglobin and histohaematins. From my viewpoint, this process would serve to extract from them what constituents might serve for the elaboration of the adrenal secretory product.

Finally, much might be learned by trying to explain all the respiratory phenomena that have been attributed by as many physiologists and clinicians to adrenin in the foregoing pages to a function other than that of pulmonary and tissue respiration.

Need I urge in the presence of all these facts that a systematic cooperation between the physiologist and the clinician, *each seeking to aid the other through the special knowledge he possesses,* would greatly hasten our knowledge of the endocrine glands? Need I urge that all recorded data, physiological and clinical—of which the foregoing are but a few on the question treated—carefully tabulated and checked, then coordinated logically, *irrespective of any preconceived theory,* might open new fields which we would all, working in harmony, cultivate?

The respiration theory is only submitted here as one of the many fields of this kind. It may die a normal death; if it does, we shall at least have learned that the soil in that one area is sterile, and that another coordination of data of the many available

may prove more fruitful. Many lines of thought may thus have to be dropped by the wayside, but the day must finally come when success will reward honest effort.

Of course, the coordination of all available data is no small task; but it is one to which I hope to devote my remaining days, with financial help the nucleus of which is available. All our members will be asked to criticize to their hearts' content and to contribute from their store of observation or special knowledge, and if the true scientific spirit is shown in suggesting possible criticisms, our Association and its journal "Endocrinology," will, I feel confident, prove a blessing to mankind in its far-reaching influence upon our knowledge of disease.

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IODIN AS THE ACTIVE PRINCIPLE OF THE THYROID GLAND

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The relation of iodin to the thyroid gland has been for many years a matter of great interest to clinicians and experimentalists, and it has long been recognized that this substance holds an important place among the constituents of the gland.

For several years the writer has been engaged in research on problems involving the thyroid, and this last spring obtained some results in the course of a series of iodin-feeding experiments which should prove of interest to clinicians and other readers of this magazine. The complete account of these experiments has appeared elsewhere (Jour. of Exp. Zoology, Abstracts, Endocrin, 1918, **2**, 200, hence only a summary will be given here.

The problem briefly stated was to test the relation of iodin to the physiological activity of the thyroid and the general problem of amphibian metamorphosis, by feeding this substance and various of its compounds to normal and thyroidless frog larvae. Most of the investigators who have dealt with the problem of the relation of iodin and its compounds to the thyroid, have used mammals as experimental material, forms, which in the author's opinion, offer no such sure and certain criteria for judging the effects of iodin administration and thyroid activity upon the organism as do frog larvae. The investigations of Gudernatsch (since followed by those of Morse, of Lenhart and of Swingle) showed that any

increased stimulation of thyroid activity, as for instance feeding extract of the gland, is at once indicated by metamorphic changes in the tadpoles. The idea was to utilize such somatic changes as an index of the effect of iodin feeding upon the physiological activity of the thyroid in the normal animals, and to see if animals whose thyroids had been removed very early in embryonic life would react to iodin.

For the experimental work, the larvae of the common leopard frog, Rana pipiens, and the toad, Bufo lentiginosus were used. The animals of all cultures came originally from the same batch of eggs, hence were of the same age. Iodin and two of its compounds were used in the original work: iodin crystals, iodoform, and potassium iodide. Since the publication of the original work, an experiment was tried in which potassium iodate was fed. The iodin crystals were ground exceedingly fine and mixed with wheat flour in the proportion of one to one-hundred, enough water was added to make a thin paste; this was allowed to dry at room temperature, and when dry finely crumbled and fed to the larvae.

The normal animals with thyroid glands intact, were started upon the iodin, KI, and iodoform diet when they were ten mm. in length; none showed indications of limb-buds. Within a few days of the first administration, the larvae fed iodin crystals showed all of the characteristic symptoms of hyperthyroidism. They had developed limb-buds, growth had ceased, bodies were emaciated, eyes bulged out, and the tails of the larvae showed signs of resorption. The control animals for this culture showed none of these body changes.

Shortly afterwards the larvae to which iodoform was fed showed marked metamorphic changes. Still later, the animals of the KI-fed culture revealed these metamorphic changes, though to a less degree than the animals of the other cultures. The reaction was much slower in regard to the time of appearance. Within two weeks of the first feeding of iodin crystals the larvae of the iodin-fed culture had completely metamorphosed. This was true of both toad and frog larvae. The animals used as controls for all of these cultures revealed no indications whatever of metamorphic changes. This same experiment with slight modifications in the method of administering iodin and its compounds was carried out with four sets of larvae. The results obtained were the same in all cases.

In the meantime, cultures of larvae, the thyroid glands of which had been removed at the four mm. stage, were started on the iodin crystal diet. These animals when first fed were ten mm. in length, and were controlled by other thyroidless and normal larvae of the same age. In a remarkably short time —five to six days,—all of the thyroidless animals showed marked signs of "hyperthyroidism." The hind legs of the animals had appeared, growth had ceased, bodies were emaciated and eyes bulgy. Within two weeks' time these thyroidless animals had come to complete metamorphosis. The controls, on the other hand, showed no indications whatever of metamorphic change. Microscopic examination of the thyroidectomized animals failed to show any vestiges of the thyroids, nor were there any signs of accessory glands.

The writer was under the impression at first that perhaps the mixture of flour, iodin and water had produced a substance which simulated the physiological action of thyroid secretion. This erroneous idea was due to the fact that in some previous experiments it had been observed that frog larvae are very soon killed when iodin crystals are placed in the container.

In order to test the point, whether it was iodin itself or the mixture of flour, iodin and water that accelerated metamorphosis, cultures of normal and thyroidless larvae were placed in weak aqueous solutions of iodin. The solutions were made by placing quantities of iodin in a few cubic centimeters of water and mixing thoroughly. Two c.c. of such a solution added to 500 c.c. of water was sufficient to bring about metamorphosis in the experimental animals. Normal and thyroidless animals living in such solutions of iodin undergo transformation from the larval to the adult form as rapidly as those fed upon the flour-iodin mixture.

Tests were also made regarding the rapidity of action of the various iodin compounds in accelerating metamorphosis. The results show that iodin crystals bring about the reaction quicker than any of the compounds used; iodoform is slightly less potent than the iodin crystals; potassium iodide is much slower than iodoform, and potassium iodate has practically no effect.

Microscopic examination of the thyroid glands of larvae reared in iodin solutions or fed on the iodin-flour mixture from the earliest feeding stage to the time of metamorphosis, shows that the thy-

roids of such animals are very much smaller than those of control larvae of the same age and held at the same size by under-feeding.

Discussion. The results of the experiments just cited appear to indicate very strongly that iodin is the active principle of the thyroid gland, and that this substance functions within the organism as a hormone itself without the intermediation of the gland. It has been shown by investigators that frog larvae whose thyroid glands have been removed early never develop into frogs, but permanently retain their larval characters. Yet iodin feeding brings about metamorphosis in these thyroidectomized animals in an abnormally short time. The fact, too, that the thyroid glands of animals fed iodin from the free feeding stage until metamorphosis, are much smaller and less developed than those of normal animals of the same age and size, is further evidence that iodin is the active principle.

The function of the thyroid, then, appears to be chiefly that of extracting and storing the physiologically active iodin, rather than elaborating an active hormone itself. That the tissues of animals are capable of utilizing iodin directly without the mediation of the gland, is shown by the results of feeding iodin to thyroidless larvae. In this connection the results of a series of experiments as yet unpublished, may be of interest. The writer has been able to demonstrate that normal blood serum acts as a solvent for iodin crystals to the extent of .00075 gms. per c.c.

All of the active substances so far extracted from thyroid tissue contain iodin, the more active they are

the more iodin they contain. This is clearly shown by Kendall's Alpha substance reported in a previous issue of this journal. The same principle holds true of goiters. The higher the iodin content of such glands, the greater their physiological activity when fed to lower animals. The work of Hunt and Seidell and of Lenhart is of interest in this connection.

The fact that iodin is capable of functioning within the organism without the gland tissue, should prove of interest to clinicians because of its bearing upon iodin therapy in the treatment of toxic goiter. If all of the symptoms of "hyperthyroidism" can be produced in thyroidless frog larvae by over-feeding with iodin, it is logical to suppose that the symptoms of "hyperthyroidism" in man are due to the same cause.

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THE EFFECT OF THE X-RAY UPON THE RESPONSE OF TADPOLES TO THYROID STIMULATION*

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INTRODUCTION

The experiments carried out by Gudernatsch (1), in 1912 upon the growth of tadpoles after thyroid gland feeding, have been repeated in this laboratory during four summer seasons. In short, Gudernatsch observed that tadpoles whose normal metamorphosis into frogs occupied from three to six months, completed this metamorphosis in five to ten days when small quantities of thyroid gland substance was added one or more times to the living water of the tadpoles. This induced early differentiation into frogs, including all the gross changes normally distributed over several months. The miniature frogs so produced, although apparently anatomically perfect, were unstable and regularly died after a few days.

In all essential respects our findings have been in accord with Gudernatsch's reports. The experiments of this laboratory were extended to include low life forms other than tadpoles and also tadpoles of certain frog species whose metamorphosis normally extends over two or more years. An effort was made to determine the influence of thyroid feedings upon the growth and differentiation of tadpoles whose natural development had been deviated by diverse procedures.

*From the Research Laboratories, Parke, Davis & Co., Detroit, Mich.

The present report concerns itself with observations made as to the development of thyroid fed tadpoles which had been exposed to the action of the X-ray.

Three distinct theories have been advanced to explain the action of the Roentgen ray upon normal tissue cells. One of these adhered to by O. Hertwig (2), and his coworkers (1912), is that the rays exert a specific destructive action upon the chromatin of the cells. Opposed to Hertwig's hypothesis is the older theory proposed by Schwartz (3), (1903), who concludes from the observation of the destructive action of the Roentgen ray upon the lecithin of egg yolk, that the injury to the cells is due to the destruction of the lecithin which they contain.

Richards (4), (1914-15), has shown that the activity of various enzymes or ferments, of both animal and vegetable origin, is susceptible to change through the influence of Roentgen rays. He concludes from his experiments that, "a short radiation has the effect of accelerating the activity of these enzymes (diastase and pepsin), while longer radiation is inhibitive. Between these strengths lies a point at which the radiation is non-effective." His observations on pepsin and diastase have since been extended to include other enzymes, the results all tending to confirm his original conclusions. He advances the theory, therefore, that, "life processes are subject to marked change under the influence of radiation, a slight exposure being accelerative in most cases, while a more intense treatment is inhibitive or destructive. As a causal factor in these effects, the demonstrable injury to the chromatin of the cell is undoubtedly important; but there are also good evi-

dences that the modifiability of enzymes under the action of the rays likewise plays a considerable part either directly or indirectly in the resulting injury."

MATERIALS AND METHODS

The tadpoles collected to participate in these experiments conformed within the acceptable limits in weight, length and in stage of development. These were maintained in large shallow trays under good condition as to light, air and aeration of living water. The food, apart from thyroid gland materials, consisted of green algae supplemented at intervals with small quantities of desiccated beef liver.

Tadpoles of the species Rana cantesbiana (bullfrog) exclusively were used. The individuals of this species normally live for at least two years in the larval state. This fact permitted the use of larvae representing two widely different stages of development. The younger group (Experiment A) was composed of tadpoles approximately one year old. At this stage the individuals exhibited no signs of differentiation into the adult form. The second group (Experiment P) was composed of tadpoles not quite two years old. These tadpoles would under the natural conditions have completed their metamorphosis before the end of the summer. The controls in this experiment actually did complete their metamorphosis, but long after the conclusion of the experiment.

In both experiments (1st and 2nd year groups) the tadpoles were divided into four equal and similar lots. Two lots in each experiment were then subjected to the rays from a Coolidge tube according to the following standardized formula:*

*The tadpoles were irradiated by Dr. George C. Chene, Detroit. Our thanks are due him for his courtesy.

	Experiment A.	Experiment D.
Current	6 milliamperes	12 milliamperes
Spark Gap	8 inches	7 inches
Distance from Anode	12 inches	12 inches
Time	2½ minutes	4 minutes

Tadpoles of Experiment A were irradiated a second time one week later, under identical conditions except that the current was doubled.

In each experiment one irradiated group and one untreated group were placed on thyroid feedings while the second irradiated group and the second control group were kept on the desiccated liver and algae diet. The thyroid was administered by scattering 100 mgms. of the commercial desiccated product in the living water.

After the death or complete metamorphosis of all the thyroid-fed tadpoles of Experiment A, and tabulation of the accrued data, the two remaining control groups were again divided. Half of each group was placed on thyroid treatment identical with that described above. This second feeding was started one month after the irradiation of the tadpoles.

The alterations in size and shape of the tadpoles incident to their development were recorded by means of a method of "shadow photography." This procedure afforded a permanent and relatively accurate record of the growth. For the purposes of carrying out this photographic mensuration a temporary dark room was constructed near the tables containing trays of tadpoles. In this dark room was placed a small shallow rectangular glass container (2″x4″) with a smooth flat bottom. Photographic printing paper was cut in such size as to fit exactly into the rectangular container. One piece of this paper was placed in this container sensitive side up. Superimposed upon the sensitive paper was a mask of

transparent celluloid upon which had been printed lines at millimeter intervals. Representative tadpoles to be measured were taken from their trays, placed in small beakers in a constant quantity of clear water. To this was added a few drops of chloroform (two to ten, depending upon the size of the tadpoles) to prevent their moving while being photographed. As soon as the tadpoles were motionless they, together with the water, were poured into the rectangular chamber previously prepared. Directly above the chamber, at about the height of 18 inches, a high power nitrogen electric lamp was placed to whose light exposure was made for two or three seconds. The motionless tadpoles resting on the millimetered mask served as a negative and the linear dimensions were directly printed out on the sensitive paper. The chloroform was found to be harmless for all except very young tadpoles. It is necessary however that immediately after being photographed the tadpoles be removed from the chloroform water. This method of recording dimensions is much less tedious than actual photography and is more rapid and less irksome than the actual measurement with dividers at frequent intervals of many hundreds of tadpoles.

TECHNICAL DATA AND COMMENTS

The effects of thyroid feeding on normal tadpoles varies with the age of the individuals. This is to be expected in view of the nature of the changes induced. In our experiments with two-year-old tadpoles (Rana cantesbiana) which had reached the stage in development immediately preceding the initiation of metamorphosis, thyroid feeding served simply to induce a premature and accelerated differentiation. Thyroid-treated tadpoles differentiated into normal frogs,

wholly indistinguishable from the controls.

In the case of one-year-old tadpoles, thyroid feeding was invariably followed by the death of the individuals. Certain somatic changes occurred before death, which were obviously similar to those changes which take place in the metamorphosis of older individuals. The alterations which were macroscopically observable occurred in approximately the following order:

1. Marked diminution in general size.
2. Alteration in the shape of the body, the rounded, well-fed larval shape giving way to the slender, trim adult form.
3. Elevation of the eye-balls above the dorsal surface.
4. Increase in width and size of the mouth.
5. Acceleration of growth of hind legs.
6. Thinning and eventual breaking through of the ventral body wall at points corresponding to the future site of the fore legs.
7. Noticeable growth of the fore leg buds.
8. Disappearance of the "fin" from the tail.
9. Shortening of the tail.

It was observed that the tadpoles all reached a certain stage in this abnormal metamorphosis, at which point death occurred. The examination of a large number of specimens preserved shortly after death demonstrated that all were very similar in the extent to which the changes outlined above had occurred, and that the date of death affords a valuable criterion as to the reaction of the tadpole to thyroid treatment. This fact has been noted before and other workers have taken the time of death of the treated tadpoles as the end-point in the quantitative estima-

tion of thyroid activity. (Marine and Rogoff, 1916, C. H. Lenhart, 1915.)

The following table indicates that in experiment A (one-year old tadpoles) the irradiated tadpoles reacted earlier than did those that were unexposed. At the outset of the experiment equal numbers (17) of tadpoles composed each of the four lots to be compared. Under thyroid stimulation both the normal tadpoles (A) and X-rayed tadpoles (A_2X) which were thyroid fed responded to thyroid stimulation and died upon attaining to a certain phase of metamorphosis, however, the X-rayed tadpoles earlier attained to this point.

TABLE I.

DATE	A Thyroid	A_2X Thyroid plus X-Ray	A_2 Control	A_4X Control plus X-Ray
5-20	17	17	17	17
5-21	17	11	17	17
5-24	(17) 14*	8	17	17
5-25	11	4	17	17
5-26	4	1	17	17
5-29	4	0	17	17
5-31	3	0	17	17
6-1	2	0	17	17
6-3	0	0	17	17

*Three killed for photographing.

The first death in the non-rayed (A) group occurred four days after the first death in the irradiated group, or when the irradiated tadpoles had been reduced to a fourth of their original number. So also the last survivor in the non-rayed group lived five days longer than did the last of the irradiated group. The exposure of tadpoles to the action of X-rays in some unknown manner determined an increase in the rapidity of their reaction to thyroid stimulation.

This conclusion is supported by photographic evidence. In figure I are shown views of average individuals from groups A_1 and A_2X. (Thyroid-fed

and thyroid fed, X-rayed, respectively.) These photographs were made on the same day and under identical conditions of focus, and of distance of the object from the lens.

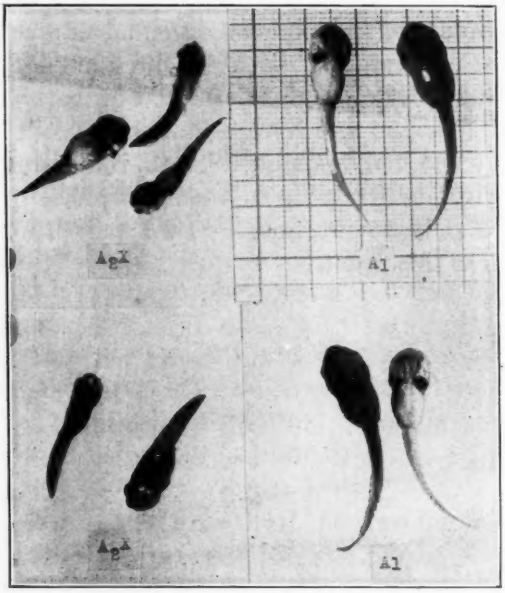

FIG. 1

Figure I. Photographs (made at the same time) of average tadpoles from group A_2X: (thyroid-fed and X-rayed) and from group A_1, (thyroid-fed but not exposed to X-rays). The relative size of the tadpoles may be estimated from the millimeter lines included in the one photograph.

The metamorphosis of the individuals in A_2X is obviously further advanced than those in A_1. This is indicated by the following points:

1. Smaller size.
2. More triangular shape.
3. More prominent eye balls.
4. Larger mouth.
5. Shorter tail.
6. Presence of fore-leg buds (discernible as

small white spots in the center of the dark area of skin rarefaction). Under the binocular microscope fore leg buds were also discernible on the tadpoles of A_1. They were much smaller, however, than on the other tadpoles.

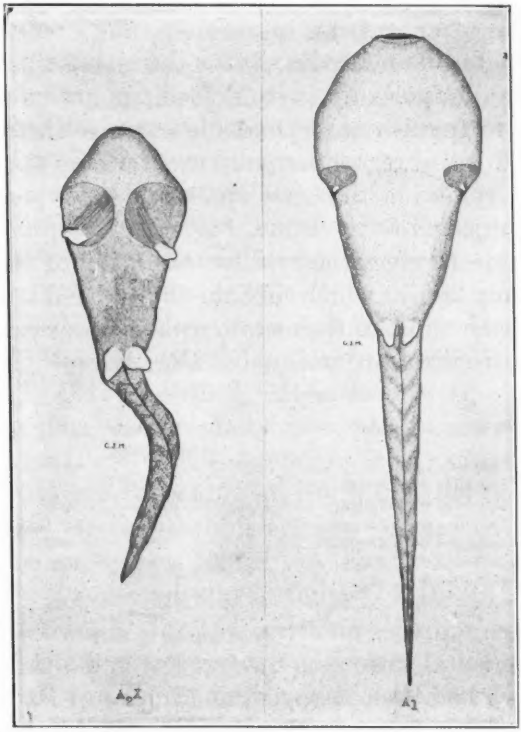

FIG. 2

Figure II. Drawings three times natural size of average tadpoles, illustrating the differences in the degree of metamorphosis attained at a certain time by members of groups A_1 and A_2X, respectively.

Groups A_3 and A_4X, which had not been thyroid-fed and which had exhibited none of the phenomena of metamorphosis were now divided and half of each group placed on thyroid feedings. As before, the

X-rayed tadpoles began to differentiate before the unexposed individuals showed any signs of change. The difference was not so marked in this case, undoubtedly because of the time (30 days) which had elapsed since exposure to the X-rays. It is significant that the irradiation was, in some measure, effective after such an interval of time.

It might be maintained that the changes induced in young tadpoles by thyroid feedings are so abnormal as to furnish no dependable index to their reactivity. For this reason tadpoles which would normally metamorphose within the space of a few months, were subjected to the same treatment.

Table II gives the relative condition of the tadpoles July 2nd, at which time the thyroid-fed tadpoles were in the midst of the metamorphosis process. The results are in accord with those already outlined.

TABLE II.

State of Metamorphosis	P_1 Thyroid	P_2 X-Ray Thyroid	P_3 X-Ray	P_4
Number of tapoles (7/2)	12	5	11	19
Number of tadpoles with 4 legs	3	3	0	0
Number of tadpoles with 3 legs	2	1	0	0
Number of tadpoles with 2 legs	7	1	11	19
Per cent of tadpoles with 4 legs	25%	60%	0%	0%
Per cent of tadpoles with 3 legs	16.7%	20%	0%	0%
Per cent of tadpoles with hind legs only	58.3%	20%	100%	100%

In the tadpoles entering into this experiment, no developmental differences were detectable in group P_2, which had been X-rayed, and in group P_4, which were normal. That is, the X-raying of the tadpoles brought about no demonstrable alteration in growth-differentiation processes. Both the X-rayed and normal tadpoles completed their metamorphosis at the anticipated time. Also, no differences were observable in the rate of response to thyroid feeding in the X-rayed tadpoles, group P_2, and the non-rayed

thyroid-fed tadpoles, group P_1. The metamorphosis of both groups was hastened, but, equally so, individuals composing both groups completed their metamorphosis and survived. In so far as the results of observation on this small number of test animals permits, it is inferred that the exposure to the X-ray exerts no gross effect upon the process of metamorphosis, either in normal tadpoles or in thyroid-fed tadpoles.

The observation that the irradiation is without demonstrable effect upon normal tadpoles is important in considering the mechanism of the reaction produced upon thyroid-fed tadpoles. Several observers have shown that following intensive exposure to X-rays there may be found a slight increase in nitrogen metabolism of normal animals. (Baermann and Linser (5), 1904, Benjamin and Van Reuss (6), 1906.) If the results recorded in this paper are due to the direct action of the rays upon metabolism, the same phenomenon also occurs in those tadpoles which received no thyroid material. The occurrence of changes in the metamorphosis of the thyroid-fed groups only, is an indication that these changes are due to an altered susceptibility on the part of the tadpoles to the thyroid hormone.

This interpretation is apparently in keeping with Richard's theory of the mode of action of the Roentgen rays. He states that a small dose of the rays serves to increase the activity of certain, and presumably of all, enzymes, while large doses produce the opposite effect. In our experiments, weak irradiation of the tadpole increased the activity of a normal hormone (thyroid), administered subsequent to the irradiation. According to Richard's theory, strong

irradiation should decrease the activity of the hormone when given under identical conditions.

In the event that further experiments prove that large doses of X-rays produce an effect opposite to the results here recorded, it may be inferred that the thyroid hormone normally acts in conjunction with the intracellular enzymes to produce the phenomena commonly associated with thyroid activity. Such an interaction has often been postulated by writers on the thyroid gland, but experimental evidence has hitherto been lacking.

SUMMARY

Selected tadpoles were subjected to the action of Roentgen rays in small amounts. Certain individuals were then treated with preparations of thyroid gland and the rate of their metamorphosis compared with the metamorphosis rate of (1) normal tadpoles, of (2) thyroid-fed tadpoles which had not been irradiated, and of (3) irradiated but not thyroid-fed tadpoles. The results of our experiments indicate that irradiation is without apparent effect upon normal tadpoles, but determines a slight but distinct increase in the susceptibility of young tadpoles to thyroid stimulation.

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THE USE OF ADRENAL PRODUCTS IN ADDISON'S DISEASE*

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Lieut. Commander M. C., U. S. Navy

Male, aged 40, American, married, was admitted to the Medico Chirurgical Hospital in October, 1911, complaining of extreme weakness, almost like that of approaching death, attacks of dangerous collapse, dyspnoea, loss of weight and marked constipation. The family history was negative.

He had a mild attack of smallpox at the age of 26; diphtheria at the age of 10 and pneumonia at the age of 27 years. Prior to 1911 brownish spots were noted on the skin of the face, neck and hands, which gradually increased in size and depth of color. In July, 1911, weakness was first observed which gradually increased, and during the preceding five years there had been a gradual loss of flesh. During 1911 he lost weight rapidly and weighed slightly less than 100 pounds when admitted to the hospital; whereas in 1906 he weighed 135 pounds.

In August, 1911, while at work in his office he suffered a collapse, which recurred in five minutes. From time to time chills followed by fever were complained of, the temperature occasionally rising to 103° F.

From the age of 11 to 14 he worked in the coal mines as a breaker boy and later in the switch yard. From the age of 34 to 43 he was a street car conductor, and is now an official in the Street Carmen's Union. For many years he chewed daily from two to three ounces of tobacco and smoked two or three cigars;

*Read before the Association for the Study of Internal Secretions, Chicago, June 10, 1918.

drank coffee to excess but avoided alcohol. Habits of eating and sleeping were markedly irregular.

Physical examination revealed emaciation; visible carotid and epigastric pulsations; diffuse apex beat and prolongation of the first sound of the heart; pulse slow, very weak and easily extinguished by slight pressure; radial and temporal arteries sclerosed; marked spinal curvature to the left from the first to the fifth dorsal, and to the right from the fifth dorsal to the second lumbar vertebra, and a roentgenogram showed the signs of ostitis, rather than tuberculosis. There was increased fremitus and impaired resonance over the apices of the lungs corroborated by an X-ray examination and interpreted as indicating healed tuberculosis. The von Pirquet test was positive. The right kidney was movable and slightly tender on pressure. The renal efficiency test showed the first hour 52%, the second hour 28%, total 80%. There were pigmented areas of the skin varying in color from light to dark brown, more marked on exposed surfaces, particularly the neck and face, also on the thighs, about the nipples and umbillicus and the scapula where the suspenders exerted pressure. The pigmented areas of skin distributed over the forearms and hands were of mahogany or bronze color, but pigmentation was absent over the spinal region which was subject to the pressure of the weight of the body while lying in bed. There were areas of leucoderma over various parts of the body, especially over the right temple, where the hair had turned white, and these areas seemed dryer than the surrounding skin. There were marked pruritis and numerous scratch lesions. The muscles were markedly flabby, relaxed and atrophied. There

was a negative history of venereal disease and a negative Wasserman reaction. The temperature was continuously subnormal, at times 96° F.

The pulse varied between 56 and 98 per minute; the heart was overacting. Examination of the blood revealed 69% erythrocytes, 74% hemaglobin and 11,200 leucocytes, of which there were 65.5% polymorphonuclears, 21.3% large lymphocytes and 8% small lymphocytes. Later a mild eosinophilia occurred which was non-parasitic and toxic in origin.

October 21st in the recumbent posture the pulse was 60 per minute, systolic pressure 80 mm. and diastolic 60 mm. Numerous urinalyses gave negative results.

The following day 1 drop of a 1 to 1000 adrenalin chlorid solution was given thrice daily.* After the third dose no change was noted in the blood pressure. After four doses of two drops each had been given, the systolic pressure was 90 mm., the diastolic 60 mm. and the patient volunteered the information that he felt somewhat stronger. On October 25th three drops of adrenalin chlorid solution were given four times daily, and the systolic pressure rose to 110 mm. and the disastolic remained 60 mm. From October 25th to November 1st, 1911, five drops of adrenalin chlorid solution were administered three times daily, after which the systolic pressure was but 100 mm. and the diastolic 70 mm. Then followed an interval of five days during which no medication was given, at the end of which time the systolic pressure was 90 mm. On November 13th, 1911, 8c.c. of an infusion of digitalis was given four times a day. After ten doses had been administered the systolic pressure was 110 mm.

*The adrenalin in all cases was administered hypodermatically.

and the diastolic 80 mm.; the first sound of the heart was somewhat blurred and the second sound at the apex was reduplicated. The digitalis was withdrawn and four days later the systolic pressure was 98 mm. and the diastolic 70 mm. On November 24th, 1911, adrenalin chlorid was given in gradually increasing doses and on December 2nd, 11 drops thrice daily were administered, causing the heart to beat violently, shaking the entire chest, and a faint, soft, mitral systolic murmur became audible. The systolic pressure was 112 mm. and the diastolic 88 mm. Adrenalin chlorid was discontinued, and four days later the murmur had disappeared, but there was marked reduplication of the second sound at the base of the heart; the systolic pressure was 110 mm. and the diastolic 90 mm.

The administration of adrenalin chlorid slightly raised the blood pressure, when therapeutic doses were given, but toxic doses were dangerous, causing cardiac dilatation. Digitalis only slightly increased the blood pressure.

In January, 1912, 15 grains of adrenal gland (B. W. & Co.) were administered three times daily. January 15th, the systolic pressure was 110 mm., the diastolic 88 mm. and the blood examination revealed a marked increase in red cells, and a *disappearance* of the leucocytosis and eosinophilia, possibly due to adrenal extract. Until discharged from the hospital in January, 1912, the systolic blood pressure varied from 102 to 110 mm., while the diastolic remained constant at 80 mm. Upon leaving the hospital he had gained 10 pounds in weight, strength was greatly increased, and the profound malaise, dyspnoea, and syncopal attacks had disappeared. Soon after re-

turning home he endured a serious mental strain in conducting a carmen's strike, apparently with no ill effect, and believing himself cured and contrary to advice discontinued the adrenal gland extract. Soon thereafter profound weakness, dyspnoea, and one attack of collapse occurred. He consulted Dr. Martin T. O'Malley of Scranton, Penna., who as a student happened to attend the clinic when this patient was presented to the class, and remembering the patient advised the prompt use of adrenal gland extract in 15 grain doses thrice daily.

Marked improvement was soon observed. Later the patient returned to his physician complaining of tachycardia, painful cramps in the muscles of the extremities, pain in the chest, dyspnoea, pulse from 110 to 140 per minute, occasional slight rises in temperature, insomnia, ocular fullness and staring eyes. At this time the patient was supposed to be taking one dram of adrenal extract thrice daily, but investigation revealed that the druggist had dispensed thyroid extract instead of suprarenal extract. Improvement promptly followed the omission of the thyroid extract and the substitution of adrenal extract. Experimentally, toxic doses of adrenal extract grs. 90 t. i. d. were administered, which caused mental and physical weakness, irritability and insomnia, which disappeared when the dose was diminished. Maximum benefit was secured from 35 grains of adrenal extract thrice daily.

During 1914 he was able to perform work with no discomfort except when the use of adrenal extract was discontinued. In January, 1914, an attack of pneumonia supervened, and for a long time the patient complained of general weakness, exhaustion

after light exertion and coldness of the hands and feet even on the hottest days. During 1915 an attack of pleurisy occurred; otherwise he felt well while taking the adrenal extract; but if it was omitted he began to lose energy, was unable to work, complained of subjective and objective coldness of the extremities, profound weakness and recurring collapse. Physical examination in January, 1915 and 1917, gave the same results as when first examined, except that strength had greatly increased. On January 15th, 1917, the systolic blood pressure was 95 mm. and the diastolic 60 mm. Blood examination showed the erythrocytes 64%, hemaglobin 60%, leucocytes 6,800; polymorphonuclears 61.6%, large lymphocytes 7.3%, small lymphocytes 25.6%, eosinophiles 3.6% basophiles 1.6%.

In October, 1917, the patient died of asthenia, following neglect, and unfortunately an autopsy could not be secured.

BLOOD PRESSURE OBSERVATION

Date	Pulse	Sys.	Dias.	Remarks:
10-21-11	60	80	60	
10-22	56	80	50	3 doses adrenalin each gtts. i. Blood
10-23	64	90	60	pressure recorded one hour after
10-24	64	110	60	third dose.
10-25	60	90	60	4 doses gtts. ii.
10-27	60	110	60	At bedside; 4 doses gtts. iii.
10-30	72	100	70	Adrenalin gtts. iv.
11-1-11	68	100	70	
11-16	76	110	80	Adrenalin gtts. v.
				Left hospital for a few days.
11-17	76	110	80	10 doses of infusion of digitalis dr. iv.
11-19	78	98	65	Reduplication.
11-20	76	98	70	No digitalis for 24 hours.
11-24	72	105	90	
11-25	84	110	90	
11-26	72	100	80	Adrenalin gtts. ii. and iii.
11-27	72	106	82	Adrenalin 2 doses, gtts. iv.
11-28	72	98	78	Adrenalin 2 doses, gtts. v.
11-29	72	104	80	Adrenalin 2 doses, gtts. vi.
11-30	72	104	84	
12-1-11	76	108	90	Adrenalin gtts. viii.
12-2	68	112	88	
12-3				Adrenalin gtts. ix.

Date	Pulse	Sys.	Dias.	Remarks:
12-4	84	110	86	Adrenalin gtts. xi. Faint mitral systolic murmur.
12-5	88	96	76	Pulse irregular; distinct mitral systolic murmur; reduplication; adrenalin omitted.
12-6	80	108	84	
12-7	96	110	82	
12-8	88	110	90	Heart regular; murumur less marked.
12-10	84	106	82	
12-11	54	110	84	No murmur; reduplication.
12-12	54	122	90	
12-13	76	108	86	Reduplication.
12-14	92	106	86	Faint mitral systolic murmur; marked reduplication.
1-15-12	60	95	60	
1-16	72	95	70	Returned home for one month.
1-17		90	80	No murmur or reduplication.
1-18		90	70	
1-19		85	70	
1-20		85	70	
1-21	78	85	72	
1-23		87	75	
1-24		95	79	
1-25		95	75	
1-29		95	80	
1-30		95	80	
1915.				
1-5-15	74	110	85	
1-11	64	100	70	
1-15	70	110	80	
1-16	74	105	80	
1-17	70	105	80	
1-18-15	70	105	80	
1-20	72	100	80	
1917.				
1-5-17		92	70	
1-15	76	95	60	

EXAMINATIONS OF THE BLOOD

1911.	Erythrocytes	Hemoglobin	Leucocytes	
Oct. 26.	69%	74%	11,200	
Nov. 13.	76%	64%	10,600	
				Polymorphonuclear 66.5%
				Large Lymphocytes 21.3%
				Small Lymphocytes 8.0%
				Eosinophiles 4.0%
				Basophiles 0.5%
Nov. 20, 1912.	77%	75%	11,000	
Jan. 16 1915.	85%	98%	6,800	
Jan. 5 1917.	82%	86%	8,000	
Jan. 15.	64%	60%	6,800	
				Polymorphonuclear 61.6%
				Large Lymphocytes 7.3%
				Small Lymphocytes 25.6%
				Eosinophiles 3.6%
				Basophiles 1.6%

In view of the existence of the classic symptoms of terminal Addison's disease it is probable that the suprarenal gland had almost entirely disappeared probably due to the advancing tuberculosis as this is the most common of all causes; and furthermore the apices of the lungs showed evidence of healed tuberculosis and the von Pirquet test was positive. The tender right kidney and the ankylosis of the vertebral joints may have been due to tuberculosis.

When first seen in October, 1911, it was believed that he was in danger of death from collapse at any time; and under the best circumstances he was expected to die within a year, whereas he did not die until six years after treatment was begun. It is fair to assume that the prolongation of life was secured by the administration of appropriate doses of the suprarenal gland extract. It is interesting to note that the adrenalin was only slightly beneficial and in toxic doses produced cardiac dilatation; that digitalis in therapeutic doses produced only slight benefit and in full therapeutic doses was detrimental. It would appear that toxic substances manufactured in the course of Addison's disease may produce leucocytosis or eosinophilia, which disappeared apparently due to the influence of adrenal extract. The influence of toxic doses of thyroid extract in one suffering from Addison's disease was an interesting involuntary experiment.

This case illustrates that marked increase in vitality and strength may be secured by suprarenal extract without as great an increase in the blood pressure as would be expected.

ABSTRACTS

220. (ADRENAL) Two cases of suprarenal disease. Osborne (O. T.), Am. J. Med. Sc. (Phila.), 1918, **156,** 202-5.

Two cases are described. In the first pigmentation and circulatory weakness were unusually pronounced. Under treatment with adrenal and pituitary tablets the circulation temporarily improved and the pigmentation greatly decreased. The patient died shortly after. Autopsy showed complete destruction of the adrenals. In the second case pigmentation also was very marked. Under treatment with adrenal tablets and iron the pigmentation largely disappeared and the circulation and weight improved. The prognosis was regarded, however, as bad. The author considers that the poor circulation did not alone account for the marked asthenia present in both cases, but that the weakness was partly intrinsic in the muscles.

—R. G. H.

221. (ADRENALS) Antibody production after partial adrenalectomy in guinea pigs. Gates (F. L.), Jour. Exp. Med. (Balt.) 1918, **27,** 725.

Experimentally it is possible to remove from three-fourths to seven-eighths of the adrenal tissue of guinea pigs without causing symptoms of adrenal insufficiency. In order to determine antibody production after partial adrenalectomy guinea pigs were immunized to bacillus typhosus or to hen corpuscles at varying intervals before or after operation, and the curves of antibody formation traced for two to three months after immunization. Comparisons with antibody curves of control animals similarly immunized failed to show that adrenalectomy had any influence upon the rise or persistence of antibodies in the blood. Acute adrenal deficiency was not deemed necessary. If the adrenal glands were the site of antibody formation or played an essential part in immunity processes, it does not seem probable that the small remainder of adrenal tissue would effect quantitatively the antibody response to a given antigen infection as do the entire normal glands. Therefore, not only are the adrenal glands not one of the important sources of typhoid agglutinins, or of hemoagglutinins or hemolysins, but they play no essential part in the mechanism by which these antibodies are produced and maintained in the body.—H. W.

222. (ADRENALS) "Le role des surrénales dans l'action du pneumogastrique sur le coeur." (The role of the suprarenals on the action of the vagus nerve on the heart). Roger (H.) Jour. de physiol. et de path. gen. (Paris), 1917, **17**, 187.

Roger removed both suprarenal glands of the rabbit by laparotomy, then after an interval of about one-half hour stimulated the peripheral stump of one divided vagus nerve. Electrical stimulation produced a more pronounced vagal inhibition of the heart and lowering of the blood pressure than is produced in controls from which the suprarenals have not been excised. The cardiac escape from vagal inhibition was later than normal and without the usual secondary rise of blood pressure above the normal level. On the slow and continuous intravenous injection of epinephrin, in a concentration and rate so adjusted as to produce no change in blood pressure or heart rate, vagal stimulation in the depsulated rabbit produced typically normal responses. The author believes that the intervention of the suprarenal glands in the normal animal is responsible for the progressively diminishing effects of repeated vagal stimulations on the heart rate and blood pressure and for the secondary rise in blood pressure following vagal inhibition.—A. L. T.

223. (ADRENALS) Sulla funzione delle capsule surrenali. (On the function of the adrenals.) Pisani, from an article of Roger. Presse méd. Nov. 22, 1917, Rivista crit. di clin. med. (Firenze) 1918, **19**, 19.

Under the influence of a violent nervous impression a sudden hyperfunction of the adrenal medulla is found with consequent increased blood pressure. If the adrenals were previously removed there is marked and steady hypotension. The excitation of the vagus, which determines a sudden, but temporary bradycardia in normal rabbits, causes a severe and durable bradycardia if the adrenals are previously removed. This would signify a reaction against the action of the vagus determined by the adrenals, which would bring forth a predominating action of the sympathetic. The problem though is not always so simple, since the same author found out that the black pigment of the adrenals is antagonistic to the action of the adrenalin.—G. V.

224. (ADRENALS) The influence of certain conditions on the rate at which epinephrin is liberated from the adrenals into the blood. Stewart (G. N.) and Rogoff (J. M.). Am. Jour. Physiol. (Balt.), 1917, **42**, 585-86.

Data elsewhere reported. See abstracts in this journal, 1917, **1**, 348; 1917, **1**, 508; 1918, **2**, 54; and 1918, **2**, 157.—L. G. K.

225. (ADRENALS) The physiology of the melanophores of the horned toad, Phrynosoma. Redfield (A. C.) Jour. Exp. Zool. (Phila.), 1918, **26**, 275.

Stimuli from the thoracic cord are carried to the adrenals and cause the secretion of adrenin which is carried by the circulation to the melanophores in the skin. This adrenin helps control the movement of pigment granules of the melanophores in the changes of color which the animal undergoes at various times.—E. R. H.

226. (ADRENALS) Über die nach zentraler Reizung zur Störung des Kohlehydratstoffwechsels führenden Vorgänge. Eine kritische Studie zur Frage: Zuckerstich und Nebennieren. (Disturbances of carbohydrate metabolism produced by central lesions.) Kahn (R. H.) Pflüger's Archiv (Bonn), 1917, **196**, 326-394.

Experiments dealing with the disturbances of carbohydrate metabolism produced by central lesions—diabetic puncture, etc.—may be grouped in 4 classes, with the following main results: (1) **Extirpation of both adrenals.** Rabbits survived many months, and subsequent diabetic puncture was not followed by glycosuria, although the glycogen content of the liver was normal. Hyperglycaemia is not produced in such animals by CO poisoning or by diuretin, nor do they exhibit emotional or salt glycosuria. Salt glycosuria is diminished in dogs and unaffected in cats. (2) **Chromaffin and adrenaline content of the suprarenals.** The adrenal gland extirpated after diabetic puncture exhibits distinct loss of chromaffin substance and adrenaline compared with the control adrenal removed before the puncture. Previous section of the corresponding splanchnic nerve in the above experiment protects the adrenal from the effect of diabetic puncture. The same phenomena after diabetic puncture are seen in the cat, ape, and dog. Cats and dogs exhibit loss of chromaffin tissue and adrenaline in the suprarenals after asphyxia and CO poisoning. The above changes persist for a considerable time after diabetic puncture and CO poisoning in rabbits and birds. The chrome affinity of the paraganglia of the abdominal aorta is diminished for a considerable time after diabetic puncture. (3) **Nervous isolation of the liver.** Section of the nerves and vessels to the liver, with the exception of the portal vein, is still followed by hyper-

glycaemia in half the cases, although the conditions are extremely unfavorable for its occurrence. Isolation of the liver and the right adrenal from the central nervous system, leaving the connections of the left adrenal intact, was almost always followed by pronounced hyperglycaemia. (4) **Adrenaline content of the blood.** Adrenaline cannot be detected by the biological method in blood vessels remote from the suprarenal veins after diabetic puncture and other central nervous excitants or after active (i.e., which produce glycosuria) subcutaneous injections of adrenaline. Blood from the vena cava opposite the suprarenal veins has an increased adrenaline content after diabetic puncture, asphyxia, etc. There is no definite increase of blood-pressure after active subcutaneous injection of adrenaline or diabetic puncture.

A critical survey of all the facts suggests that certain elements in the brain maintain a continual tonus in the liver cells via the splanchnics and the peripheral ganglia in the abdomen. This neurogenic tonus is increased by central stimulation (diabetic puncture, etc.). Other elements in the brain near to the above are to be regarded as secretory nerve centres for the chromaffin tissue and particularly for the adrenals. Their stimulation leads to an increased output of adrenaline, which reaches the liver cells by the portal vein and hepatic artery. Excitation travels via the splanchnic and peripheral sympathetic ganglia or direct. Stimulation of the central nervous elements causes simultaneous increase in the neurogenic tone of the liver cells on the one hand, and an increased inner secretion of the chromaffin tissue on the other. Both together cause glycogen mobilisation with hyperglycaemia and glycosuria. Increased tonus of the liver cells is not a sine qua non for the disturbances of carbohydrate metabolism, however, and similarly under favorable conditions increased tonus alone is sufficient to produce abnormal glycogen cleavage in the liver and slight hyperglycaemia.—Physiol. Abst., 1918, **3**, 130-31.

227. (ADRENIN) Adrenalin content of suprarenals after death from beriberi. Ono (S.) Tokyo Igakukai Zasshi, 1917, **31**, 1-10. Jap. Med. Lit. (Seoul), 1918, **3**, 26.

On the basis of the post-mortem examination of ten acute beriberi cases, and of two which occurred during pregnancy, the author finds a medullary hypertrophy of the suprarenal and an increased adrenalin content. The chemical examination was made by the Comessatti method and the average for the left gland was 14.96 mg. It is as yet unknown what relation exists between the clinical manifestations of beriberi, especially

of the acute type, and this adrenalin-hyperfunction.—Quoted. See No. 97, p. 162, Vol. II Endocrinol.

228. (ADRENIN) Adrenalin injections, and their effect upon the viscosity of the blood. Yamada (S.), Chugai Iji Shimpo, 1917, No. 893, pp. 669-75. Jap. Med. Lit. (Seoul), 1918, **3,** 23.

A rise in the viscosity of the blood was noted about 10 to 30 minutes after the injection of adrenin, which gradually decreased again in a few minutes. After a second injection the reaction occurred more slowly, in 50 to 80 minutes. The reaction was not constant in all the persons examined.—Quoted.

229. (ADRENIN) A method for maintaining an artificial circulation through the tibia of the dog, with a demonstration of the vasomotor control of the marrow vessels. Drinker (C. K.) and Drinker (K. R.). Am. Jour. Physiol. (Balt.), 1916, **40,** 514-521.

A method of perfusing bone marrow is described, and the existence of vasomotor nerves to the marrow is demonstrated. Electrical stimulation of these nerves or the injection of epinephrin into the perfusion fluid causes vaso-constriction. In one case after the administration of ergotoxin phosphate "a slight but rather doubtful degree of active dilatation was secured." The authors do not consider this reliable evidence for the existence of an active dilator mechanism.—L. G. K.

230. (ADRENIN) Constriction from adrenalin acting upon sympathetic and dorsal root ganglia. Hartman (F. A.), Kilborn (L. G.) and Fraser (L.), Am. Jour. Physiol. (Balt.), 1918, **46,** 521-525.

It was shown by the methods used in previous researches (see abstracts in Endocrinol., 1917, **1,** 510, and 1918, **2,** 160, abst. 91) that adrenalin not only causes dilatation, but occasionally can produce constriction also in the hind limb by acting upon the sympathetic and dorsal root ganglia, and in the small intestine by acting upon the superior mesenteric and dorsal root ganglia.—L. G. K.

231. (ADRENIN) Die Hemmung der Kochsalzausscheidung im Harn durch Adrenalin. (Inhibition of sodium chlorid excretion through the kidney by adrenin). Buleke (W.), and Weis (P.), Deutsches Arch. f. klin. Med. (Leipzig), 1917, **123,** 163-203.

Adrenin given subcutaneously in man and rabbits inhibits the NaCl output in the urine. The same occurs on intravenously injecting Ringer's solution to which adrenaline has been added. This leads to retention of salt. The urinary nitrogen runs parallel to the NaCl in rabbits, and in man depends on the amount of urine formed. The kidney itself is the point of attack. It does not appear to be a purely vascular effect, but the kidney cells are affected, and in disease they are more sensitive to the action of adrenaline than they are normally.—Physiol. Abst., 1918, **3,** 130.

232. (ADRENIN) Disappearance of the pigment in the melanophore of Philippine house lizards. Ruth (E. S.) and Gibson (R. B.) Philippine Jour. Sci. (Manila), 1917, **12B,** 181-188.

These pigment cells neither contract nor expand. The color is discharged by adrenaline, both in vivo and in vitro. Bleaching occurs when the lizard is in white surroundings, and it is assumed that the pigment varies during life owing to the action of a hormone (probably adrenaline).—Chem. Abstr.

233. (ADRENIN) L'azione dell'iodio e dell'adrenalina studiata su cellule viventi fuori dell'organismo. (Effect of iodin and of adrenin in tissue cultures.) Cervello (V.) and Levi (G.), Arch. di fisiol. (Firenze), 1917, **15,** 219-228.

Tissues from embryo chicks grow well in iodised plasma. Adrenaline is not favorable to such growth.—Physiol. Abst., 1918, **3,** 55.

234. (ADRENIN) On the adrenalin in the blood of one who is suffering from a primary glaucoma. Kusama (K.) Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo 1917, **17,** 137-157.

The author employed Trendelenburg's test for comparing the amount of adrenin present in the blood of healthy persons (ten cases) with that in the blood of thirteen patients suffering from glaucoma. The adrenin content was found to be decreased in the blood of the latter, and therefore, contrary to the belief of some investigators, the rise in blood pressure in glaucoma is not due to an increased output of adrenin. A more marked reduction was found to occur in cases of chronic inflammatory than in acute inflammatory or absolute glaucoma.

—L. G. K.

235. (ADRENIN) The action of the autonomic drugs on the surviving stomach. Smith (M. J.) Am. Jour. Physiol. (Balt.), 1918, **46,** 232-43.

These experiments were carried out on strips of the surviving stomach suspended in Tyrode's solution. The drugs were added in definite amounts to the solution containing the strip. Strips were taken from the following regions of the stomach—antrum, perantrum, body and fundus. Longitudinal, circular and oblique strips were used.

Pilocarpine was found to cause a contraction of all regions of the surviving stomach of the guinea-pig, rabbit, cat, dog and human subject. Atropine antagonizes the action of pilocarpine and produces a relaxation. Nicotine produces a similar effect to pilocarpine, except that the fundus and cardiac sphincter of the cat's stomach may relax, and the antrum and body of the rabbit's stomach may slightly relax before contracting.

The reaction of the different parts of the stomach to epinephrin may be relaxation (cat and human), or relaxation of some parts and contraction of others (guinea-pig, rabbit, dog). The reaction of the sphincters to epinephrin is always that of contraction. After ergotoxine those regions of the dog's stomach that contract from epinephrin may relax from administration of adrenin.

The author concludes that the sympathetic innervation of the stomach is inhibitory in the cat and in man, but inhibitory in certain regions only while predominantly augmentory in other regions of the stomach of the guinea-pig, rabbit and dog.

—L. G. K.

236. (ADRENIN) The effect of adrenalin on the irritability and contractility of mammalian nerve muscle preparations after death. Gruber (C. M.) and Fellows (A. P.) Am. Jour. Physiol. (Balt.), 1918, **46**, 472-477.

The tibialis anticus muscles of the cat were perfused with warm Ringer's solution containing only the oxygen absorbed from the air. The animal was killed with ether at the commencement of the perfusion. The nerve was stimulated by means of a Sherrington shielded electrode. The author found that the addition of adrenin to the perfusion fluid at varying intervals after the death of the animal increased both the muscular activity (height of contraction) and the irritability (decreased threshold of stimulus) of the nerve muscle preparation to electrical excitation. Adrenin therefore affects dying muscles in a similar manner to fatigued muscles.

Three possible points of action of the adrenin are mentioned: (a) It may assist or hasten the conversion of glycogen into sugar. (b) It may help to transform fatigue products by hastening the reconversion of lactic acid into sugar. (c) It

may assist in the destruction of fatigue products by increasing the rapidity of the oxidation of lactic acid into carbon dioxide and water.—L. G. K.

237. (ADRENIN) The effects of adrenin on the distribution of the blood. VII. Venous discharge from the adrenal glands. Gunning (R. E. L.) Am. Jour. Physiol. (Balt.), 1918, **46**, 362-365.

The author found that the intravenous injection of adrenin produced no active changes in the venous outflow of the adrenal glands, and therefore concludes that the splanchnic nerves carry no vasomotor fibres to the adrenals.—L. G. K.

238. (ADRENIN) The inhibitory effect of adrenalin upon the spinchter muscle of the iris. Joseph (D. R.), Am. Jour. Physiol. (Balt.), 1917, **42**, 608.

Adrenalin solutions of various concentrations when applied to the spinchter pupillae after either partial or complete excision of the muscle cause a prompt and unmistakable relaxation. The relaxation is maximal with stronger solutions. (1:1000 to 1:100,000), but only partial with very dilute solutions (1:10,000,000). The duration of the effect varies directly with the concentration. The spinchter muscles of the bovine, swine, sheep, goat and human irises were tested. In its response to adrenalin the spinchter of the iris resembles the intestinal strip.—L. G. K.

239. (ADRENIN) Über der Adrenalingehalt der Nebenniere des Menschen bei verschiedenen Todeursachen. (Adrenin content of human adrenals after death by various causes.) Lucksch (F.), Virchow's Archiv (Berlin), 1917, **223**, 290-300.

The normal amount of adrenaline is 4 mg. per gr. of dry adrenal weight. This figure falls in infectious and other diseases, and may reach 0.35 mg. or in infants 0.13. In Addison's disease the figure is lowest, in nephritis the highest.—Physiol. Abst., 1918, **3**, 130.

240. (ADRENIN, PITUITRIN) The regulation of renal activity. VII. The balance between the regulation by adrenalin and by pituitrin. Addis (T.), Shevky (A. E.) and Bevier (G.) Am. Jour. Physiol. (Balt.), 1918, **46**, 129-146.

See previous abstracts in Endocrinology, 1918, **2**, 161, 162, 189.

The subcutaneous injection of amounts of adrenalin which increase the urea excreting activity of the kidney, and of amounts of pituitrin which depress that activity, have no effect when they are injected together in a certain balanced proportion. All grades of stimulation or depression may be induced by the injection of mixtures of adrenalin and pituitrin in which this balance is deflected by a preponderance of one or the other. In the rabbit the removal of both suprarenal glands is followed by a depression of the urea excreting activity of the kidney, which is greater than that which follows control operations in which the suprarenals are not removed.

The authors conclude that under physiological conditions the urea excreting activity of the kidney is determined by two main factors. There is a fixed and mechanical regulation through the urea concentration of the blood, but there is also another and overruling type of regulation which acts through the medium of the central nervous system. It is suggested that variations in the balance between the rates of secretion of the active principles of the adrenal and pituitary glands may play a part in regulating this nervous mechanism.—L. G. K.

241. **(ADRENIN PITUITRIN) Azione di varie sostanze, e specialmente della pilocarpina e della atropina sopra alcuni organi muscolari lisci. (Action of various substances on smooth muscle)** Bottazzi (F.), Atti d. r. acc. medico-chir. (Napoli), 1917, reprint, pp. 33.

Pilocarpine increases the tone of various intestinal preparations, most of all the dog's small intestine, but the effect is always completely annulled by atropine. The effects of these alkaloids on the retractor penis muscle are very uncertain and inconstant (in contrast to de Zilva's experiments, which could not be reproduced). Their effect on the uterus is likewise irregular. On the other hand, the uterus is affected in a constant manner by adrenaline, p-hydroxyphenylethylamine, B-iminazolylethylamine, and hypophysine. The first two caused relaxation of the non-pregnant, and contraction of the pregnant uterus of the bitch. In the cat they always caused contraction, which is not in agreement with the results of Cushny and others. Speculating on the adrenaline-ergotoxine vasomotor reversal, and the fact that adrenaline always causes contraction of the pregnant uterus, the author suggests that the inhibitory innervation of the organ may in pregnancy be paralysed by substances as yet unknown.—Physiol. Abst., 1918, **3**, 103.

242. **(AUTONOMIC NERV. SYST.) Asthma considered in its relation to the vegetative nervous system.** Pottenger (F. M.) Am. J. Med. Sc. (Phila.), 1918, **155**, 417-24.

A general discussion of the etiology of asthma relating the malady particularly to reflexes mediated through the vagus nerves.—R. G. H.

243. (AUTONOMIC N. S.) Le azioni antagonistiche autonomi. (The action of antagonistic autonomics.) Spadolini (I.), Arch. di. fisiol. (Firenze), 1917, **15,** 1-167.

Rather more than one-half of the paper is devoted to a critical review of earlier work, the remainder to observations on the autonomic innervation of the urinary bladder and of the small intestine. Excitation of the hypogastric nerves in dog and cat may lead either to inhibition or to augmentation of the vesical contractions according as the stimulus is weak or is strong respectively. Similarly, adrenaline in small doses may inhibit, whilst in larger doses its effect may be the converse. The nervi erigentes are motor in function. Analogous effects were observed on the small intestine, when the vagi or the splanchnics were stimulated. Excitation of either of these nerves may produce either inhibition or the converse, according to the intensity of the stimulus. The writer regards the parasympathetic fibres (of vagi and nervi erigentes) as being responsible for relatively rapid contractions, and the sympathetic fibres as being pre-eminently tonic in function. The response to a given stimulus is in any case a function of the condition of the muscle.—Physiol. Abst., 1918, **3,** 18.

244. (AUTONOMIC NERV. SYST.) Pharmacodynamic examination of the vegetative nervous system in typhoid fever. Matsuo (I.) and Murakami (J.). Arch. Int. Med. (Chgo.) 1918, **21,** 399-410.

A study was made of the reactions of typhoid patients to pilocarpine, atropine and adrenin. In 38 cases 14 showed abnormal irritability of the parasympathetic system and 11 cases showed hyperirritability of the sympathetics. Three cases were sensitive to all drugs, 7 cases were sensitive to pilocarpine and adrenin and 3 only to pilocarpine.

245. BONE MARROW, Internal secretion of. Ord. (G. W.), Lancet (Lond.), 1918 **1,** 385.

The suggestion is made that marrow does something more than minister to bone nutrition. Some bones have little or no marrow, and the way it is so safely housed, and the serious results (shock, death, etc.) that follow extensive bone removal, are considered to support this view.—Physiol. Abst., 1918, **3,** 132.

246. (CORPUS LUTEUM) The non-effect of corpus luteum preparations on the ovulation cycle of the rat. Corner (G. W.) and Hurni (F. H.) Am. Jour. Physiol. (Balt.), 1918, **46**, 483-486.

On each of the four days following littering a benzidine compound, staining the corpora lutea blue, was injected intra-abdominally into rats. This was followed by the intra-abdominal administration of dessicated corpus luteum substance in normal saline, given every other day for twenty days. The rats were then killed and the ovaries examined in serial sections, the number of stained and unstained corpora lutea being compared. It was found that in all cases ovulation had continued unchecked, showing that the intra-peritoneal injection of mammalian corpus luteum substance does not inhibit ovulation in the rat.—L. G. K.

247. (DERCUM'S DISEASE-ADRENIN) Istografia, Istochimica e Patogenesi dei lipomi di Dercum. (Histology, histo-chemistry and pathogenesis of Dercum's lipomata.) Martelli (C.) Tumori (Rome) 1918, **6**, 1.

The author begins with an accurate description of the severe symptoms determined by the formation of such lipomata, and insists on the good effects brought about by adrenalin therapy during the following asthenic period.

Upon examination of one of these tumors the author found it histologically like the common lipoma, made of adult fatty cells. There are, besides, hyperaemic zones with perivascular micro-cellular infiltrations, due to inflammatory processes. He finds also mononeuritis of the few nervous fibres, and an elastic, pre-colloid hypertrophy of the tumor, which makes its consistency more dense than that of the surrounding fatty tissue.

The chemical composition of the lipomatous cells is chiefly that of neutral fat mixed (in 2 to 3 per cent of said cells) with fatty acids, which show also a granular appearance in the interstitial tissue. Common lipoids are found in greater amount either as cuticle and lipoid grains, or spread in the subcuticular stratum at the periphery of the adipose vesicle. Very scanty, if present, are the special lipoids as lecitine, lipochromes and cholesterine. There is no calcium.

Compared with the common lipomata, Dercum's lipoma does not show either embryonal elements or lecithinic cells, or phenomena of atrophy. It appears like an accumulation of adult fatty vesicles (at rest), quite like those of the normal subcutaneous adipose tissue, only a little smaller, pressed to-

gether and rich in lipoids with hyperemic foci and microcellular infiltrations inserted.

As for the pathogenesis the author claims that such lipomata are the expression of disturbed equilibrium of lipogenesis (connected with multiple endocrine-sympathetic disfunctions—mostly suprarenal) which forms in the subcutaneous connective tissue in parts rich in elastic tissue. This formation may be either slow, as in the indolent lipomata, or (very seldom) sudden and painful—in form of an anaphylactic discharge (Dercum's)—almost as if the organism were to free itself of a toxic product (probably lipoid and very likely in connection with suprarenal insufficiency) and were to localize such product under form of lipomata in the subcutaneous tissue.—G. V.

248. (DIABETES) Diabetic polyneuritis. Pitres (A.) and Marchand (L.) Prog. méd. (Paris), 1917, **32,** 295.

A case is described at length. The prognosis is usually favorable.

249. (DIABETES) The application of the Auer-Kleiner morphine test in human diabetes. Epstein (A. A.) Proc. Soc. Exp. Biol. and Med. (N. Y.), 1918, **15,** 89-90.

An attempt was made to utilize as a clinical test for latent diabetes the fact that morphine in dogs causes a rise in the blood-sugar. Within the practicable limits of dosage no unequivocal effect was produced in man.—R. G. H.

250. (DIABETES) The rate of dialysis of diabetic blood-sugar. Kleiner (I. S.), Proc. Soc. Exp. Biol. and Med. (N. Y.), 1918, **15,** 81-2.

The fact that the sugar of diabetic blood was found to diffuse less readily than a similar concentration of sugar in normal blood is thought to indicate that the diabetic blood-sugar is held in some sort of loose combination.—R. G. H.

251. DIABETES, Salt metabolism in. Beard (A. H.) Arch. Int. Med. (Chgo.) 1918, **21,** 716-39.

This paper is a report of an elaborate study of the problem. Two points of general interest were brought out: 1. Increase of weight on unrestricted chlorids is invariably associated with their retention. The edema usually disappears following the disappearance of the glycosuria. 2. Sodium bicarbonate ad-

ministration has no constant influence on carbohydrate tolerance in diabetes.—R. G. H.

252. (DIABETES) Über die Kohlenhydratverwertung des normalen und diabetischen Muskel. (Carbohydrate content of normal and diabetic muscle)—I. Forschbach (J.) and Schaffer (H.), Arch. exp. Path. Pharm. (Leipzig), 1918, **82,** 344-367.

It is generally supposed that the tissues in diabetes are sugar-laden, and this is regarded as an explanation of their lessened resistance towards infective agents. This view is disputed. In the muscles the sugar content is not increased in diabetes.—Physiol. Abst., 1918, **3,** 119.

253. DIABETES INSIPIDUS, A case of, as sequel to gunshot wound of the head. Graham (E. A.) Ann. Surg. (Phila.), 1917, **66,** 529.

Additional support that diabetes insipidus is an expression of a disturbed function of the hypophysis, or neighboring tissue.

254. DIABETES INSIPIDUS, Control of symptoms of by subcutaneous injections of extracts of hypophysis cerebri. Barker (L. F.) and Mosenthal (H. O.), Jour. Urol. (Balt.), 1917, **1,** 449.

A most favorable effect was obtained by this method. Tethelin and adrenaline were of no value.

255. DIABETES INSIPIDUS from hemorrhage in the neurohypophysis and peduncle. Luzzatto. Lo Sperimentale, Nos. V-VI, 1917. Rivista crit. di clin. med. (Firenze) 1918, **19,** 91.

A case of polydipsia and polyuria with progressive cachexia is reported by Luzzato, who at the post-mortem examination found an old hemorrhage destroying the posterior lobe of the hyophysis and cutting the peduncle at its entrance into the posterior lobe. The surrounding parts of the brain do not show any abnormality, so that the author brings out such a finding as a severe objection against Camus and Roussy's theory (Lesions of the optopeduncular basilar region as a cause of Diabetes insipidus).—G. V.

256. DIABETES MELLITUS, Influence of the war on. v. Noorden (C.) Med. Klinik (Berlin), 1916, **12,** 991.

Nervous stress alone does not elicit diabetes, but it aggravates the condition, probably by whipping up the adrenals.—Chem. Abstr.

257. DUCTLESS GLANDS and War.

The Medical Research Committee call attention to overactivity of the endocrine organs in times of intense stimulation. In the siege of Paris (1871) Graves' disease was common. So far in the present war its frequent sequela, myxœdema, has not had time to occur. Alexander (Med. Klinik, 1917, **13,** 994-996), notes a case of Graves' disease following a bomb explosion. Reference is also drawn to the following paper in relation to the adrenal glands: Ramond and Francois (Bull. et mém. soc. méd. des hop. de Paris, 1917 [3], **41,** 1001-1003), who have noted the frequency of Addison's disease; here adrenal exhaustion increases liability to tubercular infection. Among other points noted is that in war cases the blood-pressure is well sustained until near the end.—Physiol. Abst., 1918, **3,** 50.

258. (ENDOCRINE GLANDS) Animal diastases. II. Blood diastase of rabbits. Watanabe (C. K.), Am. Jour. Physiol. (Balt.), 1917, **45,** 30-43.

This is increased by the intravenous injection of human saliva, parenteral administration of starch (slightly, amylase also appearing in the urine), intravenous or intraperitoneal injection of $NaHCO_3$ in large doses. The latter also causes hyperglycæmia. Ether anaesthesia and adrenaline cause hyperglycaemia, but no change in the diastase of the blood. Pituitrin, ingestion of HCl, small doses of Na_2CO_3, and thyroid feeding have no appreciable effect on blood-sugar or diastase.

259. (ENDOCRINE GLANDS) Azione degli estratti di ghiandole endocrine sui processi di regenerazione. (Effect of endocrine gland extracts on regeneration). Piccoli (G.), Arch. di fisiol. (Firenze), 1917, **15,** 199-208.

The tails of newts were amputated a week before injecting gland extracts. Taking the number of dividing nuclei as the criterion, an increase was noted with pituitary and adrenal (small dose) extracts; a diminution occurred with thyroid and a large dose of adrenal extract, and no change with extract of testis. Taking the rate of growth of the stump as the criterion, adrenal, thyroid, and testicular extracts all caused a diminution; a small dose of pituitary produced no change, but a large dose caused an increase.—Physiol. Abst., 1918, **3,** 52.

260. GLYCOSURIA, renal. Beard (A. H.) and Grave (F.) Arch. Int. Med. (Chgo.) 1918, **21,** 705-15.

The continued presence of any considerable amount of sugar in the urine is nearly always indicative of insufficiency of the endocrine function of the pancreas. Beard and Grave present a detailed study of a case of glycosuria, however, of renal origin. In order to differentiate a renal from a pancreatic glycosuria it is necessary to demonstrate: 1. A urine containing dextrose in amount unchanged to any great extent by fluctuations of carbohydrate intake. 2. A blood sugar of normal percentage. Cases of true renal diabetes are very rare. —R. G. H.

261. (HORMONES). The destruction of hormones, proenzymes, and enzymes, by ultra-violet radiation. Burge (W. E.). Am. Jour. Physiol. (Balt.), 1916, **40,** 137-138.

Data elsewhere reported. See abstract in this Journal, 1917, **1,** 66.—L. G. K.

262. HYPERNEPHROMA, Vaginal metastases of. Gellhorn (G.) Am. J. M. Sc. (Phila.), 1918, **156,** 94-104.

Metastases of hypernephromata in the vaginal wall are rare, the author having found only nine cases in the literature. A tenth case is reported.—R. G. H.

263. (HYPOPHYSIS) Abuso de la pituitrina (Abuse of pituitrin) Artega (J. F.), Rev. Med. y Ciruj. (Havana), 1916, **21,** 71-2.

Two cases are described in which reckless use of pituitary injections led to unhappy results—in one case a barely averted rupture of the uterus and in one to a tear of an old scar in the cervix, causing profuse hemorrhage. The author thinks that none but competent specialists should be allowed to use medicaments of such potency.—R. G. H.

264. (HYPOPHYSIS) An improved apparatus for testing the activity of drugs on the isolated uterus. Pittenger (P. S.), Jour. Am. Pharm. Assoc. (Easton, Pa.), 1918, **7,** 512.

A detailed description of the author's apparatus and method for testing pituitary preparations on the isolated uterus. —F. F.

265. HYPOPHYSIS cerebri: its structure and development. Parker (K. M.), Sci. Progress (Lond.), 1918, No. 47, 450-464.

A review of recent work. The physiological side of the subject is only cursorily mentioned.—Physiol. Abst., 1918, **3,** 52.

266. (HYPOPHYSIS) Hypophyseal tumors through the intradural approach. Adson (A. W.), Jour. A. M. A., 1918, **71,** 721-26.

The technique of this operation is described and illustrated. The results of six cases are reported and the advantages of this method of operation pointed out.—R. G. H.

267. (HYPOPHYSIS) Physiological assay method of the U. S. P. IX. Pittenger (P. S.), Jour. Am. Pharm. Assoc. (Easton, Pa.), 1917, **6,** 871.

Pittenger states that more concordant results are obtained, in the standardization of liquor hypophysis, by employing the whole one horn of the uterus of a 350 to 425 gram guinea pig, instead of only a segment of the one horn from a 250 gram guinea pig. The author suggests improvements in the lever arrangement by means of which the uterine contractions are recorded on the kymograph.—F. F.

268. (HYPOPHYSIS) Pituitary disturbance in its relation to the psychoses of adolesence. Tucker (B. R.), Jour. A. M. A., 1918, **71,** 330-32.

Author's abstract previously published as No. 127, Endocrinology, 1918, **2,** 171.

269. (HYPOPHYSIS) Preliminary note on the value of beta-iminazolylethylamin hydrochloride as a standard for testing pituitary extracts. Pittenger (P. S.) and Vanderkleed (C. E.) Jour. Am. Pharm. Assoc. (Easton, Pa.), 1917, **6,** 131.

A criticism of the standard adopted by the U. S. Pharmacopeia, ninth revision, for liquor hypophysis.—F. F.

270. (HYPOPHYSIS) Production of transplantable growth. Erdmann (Rhoda), Proc. Soc. Exp. Biol. and Med. (N. Y.) 1918, **15,** 96.

The stimulating effect of tethelin upon new growths was shown by the author in the following manner: Embryonic heart tissue of the chicken is cultivated after twelve days' incubation, for three days in a plasma medium. Then pieces 1 mm. square are implanted subcutaneously in a fowl. After ten days small protuberances develop which upon section appear as

cystic formations. If one of these protuberances is treated with injections of tethelin it becomes three times as large as its untreated neighbor.—R. G. H.

271. (HYPOPHYSIS) Recherches experimentales sur l'hypophyse de la grenouille. (Experimental researches on the hypophysis of the frog). Houssay (B. A.) Jour. de physiol. et de path. gen. (Paris), 1917, **17,** 406.

The hypophysis of the frog (Leptodactylus ocellatus) is made up of the three parts: glandular, intermediary and nervous portions. The glandular part contains both acidophil and chromophil cells. Hypophysectomy was performed by an incision through the palate, leaving a flap of bone and membranes with which to close the wound after the operation is completed. Total hypophysectomy frequently, but not invariably is fatal within a few days. Occasionally animals survive for many weeks. The same operative manipulations without removal of the gland is not fatal. A previous grafting of the hypophysis appeared to lessen the mortality. Reflex excitability is not diminished. Hypophyseal extract from the frog exerts a pressor effect, increases cardiac systole, acts as a galactagogue, dilates renal vessels and produces diuresis, being thus analogous to the action of hypophyseal extract of higher vertebrates.—A. L. T.

272. (HYPOPHYSIS) The pituitary in relation to loss of memory and inability to concentrate the attention. Basile (G.) Policlinico (Rome), 1917, **24,** 458.

Certain cases showed more or less loss of memory, insomnia and an inability to concentrate the attention in association with diseased sphenoidal sinus or tumors in the nasopharynx. It is regarded as probable that such lesions involved the pituitary body, giving rise to the mental symptoms.—Physiol. Abst., 1918, **3,** 132.

273. (HYPOPHYSIS) Über das Vorkommen von Reisenzellen in der Hypophyse. (Giant cells in the hypophysis.) Simmonds (H.) Virchow's Archiv. (Berlin), 1917, **223,** 281-90.

True giant cells were noted in certain conditions, mainly in elderly women.—Physiol. Abst., 1913, **3,** 132.

274. HYPOPHYSIS, THYROID AND PARATHYROIDS, Studies of. Kamo (K.) Kyoto Igaku Zasshi, 1917, **14,** 1-39. Jap. Med. Lit. (Seoul), 1918, **3,** 33-34.

The hypophyses of puppies thyroidectomized 1½ to 5 months previously were always found to be hypertrophied even to 2½ times the usual size, the anterior lobe being chiefly affected. Marked histological changes also occurred, among which may be mentioned the appearance of enlarged eosin-staining granular cells. These were not present in adult animals similarly treated, although the hypophyses were enlarged. No special alteration took place in the middle lobe.

The hypophyses of parathyroidectomized dogs and puppies were not particularly changed in the anterior lobe, but the middle lobe showed an increase in volume in puppies and an increase in colloid substance in full-grown dogs.

The parathyroids remaining after thyroidectomy were always hypertrophied, but exhibited no cellular changes. A thyroid rest, overlooked in total thyroid-parathyroidectomy, underwent great hypertrophy; the follicles were very unequal in size and contained a thin fluid.

Adrenalin glycosuria was greatly decreased by total thyroidectomy in dogs, and adrenalin had no toxic action on these animals when given in reasonable doses. It was, however, quite toxic for parathyroidectomized dogs, and the violent symptoms of tetany were suppressed by the administration of thyroid extract.

The histological and physiological independence of the thyroid and parathyroids was considered proven, even though at times there may seem to be antagonism and at other times a complimentary action between them.—L. G. K.

275. INTERNAL SECRETIONS, General physiological relation of. Sewall (H.) Col. Med. (Denver), 1918, **15**, 45-47.

A general discussion of well-known data.—R. G. H.

276. (INTERNAL SECRETIONS) Internal Secretion in learning. Dunlap (K.), Psychobiology (Balt.), 1917, **1**, 61-64.

The author suggests as a hypothesis that the direct influence of emotion on action and particularly the influence of pleasure (or satisfaction) and pain (or dissatisfaction) on the formation of habits are due to the "fixing effects" of a hormone. The nervous discharge is supposed to leave an arc or certain important points in the arc in such a condition chemically that this unknown hormone, which is discharged into the blood during pleasure, may a few moments later "fix" it. The effects of pain in preventing the fixing of the reaction may likewise be due to a negativing agent (perhaps adrenalin).

The theory is entirely speculative and as yet unsupported by experimental evidence.—L. G. K.

277. INTERNAL SECRETIONS, Progress of the year in the study of, with report of five cases. Ruggles (A. H.) Rhode Island Med. Jour. (Providence), 1917, **1,** 170-75.

A brief review of some of the recent literature. Five cases are reported with a few superficial details. They are: (1) Thyroid intoxication with mental symptoms; (2) Hyperthyroidism following extirpation of ovaries, treated with ovarian substance; (3) Adrenal insufficiency (?); (4) Adrenal insufficiency treated with suprarenal tablets; (5) Anemia with adrenal insufficiency. The diagnosis of adrenal insufficiency was apparently made largely on the presence of Sergent's "White line."—R. G. H.

278. INTERNAL SECRETIONS, Some relations between the emotions and glands of. Cannon (W. B.) Jour. Lancet (Minneapolis) 1916, **36,** 685-88.

An address detailing the well-known work of Cannon and his collaborators on the relation of the emotions to adrenal and thyroid discharge.—R. G. H.

279. INTERNAL SECRETIONS, The. Guenther (A. C.) Nebr. State M. J. (Norfolk, Nebr.) 1918, **3,** 15-19.

A general review of the more important literature. Nothing new.—R. G. H.

280. (INTERNAL SECRETIONS) The defective child from the standpoint of the internal secretions. Harrower (H. R.) So. Cal. Pract. (Los Angeles) 1917, **32,** 101-106.

An enthusiastic general discussion of the topic.—R. G. H.

281. (INTERNAL SECRETIONS) The diagnosis of the internal secretory disorders. Harrower (H. R.) Med. Herald (St. Joseph, Mo.), 1916, **35,** 186-88, 217-19, 257-60, 295-98, 333-37, 361-65. Also published in Western Med. Times (Denver) 1916, **35,** 502-4, 558-61, **36,** 9.

Preliminary serial publication of material which afterward appeared in book form.—R. G. H.

282. INTERNAL SECRETIONS, The relations of, to neurology and psychiatry. Hammes (E. M.) Jour. Lancet (Minneapolis), 1916, **36,** 449-52.

An interesting general discussion of the topic with description of three cases illustrating respectively: hypothyroidism; hyperthyroidism, associated with insanity (melancholia), and partial gonadectomy with hypogenital symptoms benefited by testicular extract.—R. G. H.

283. (INTERNAL SECRETIONS) The activation of muscle catalase by liver. Burnett (T. C.) Am. Jour. Physiol. (Balt.), 1918, **46,** 63-66.

In these experiments the liver and leg muscles of the rat were used as being at the two ends of the scale of catalytic activity, the liver being the most active and muscle the least (excepting the brain). Both were perfused till free from blood by saline solution introduced through the aorta. The tissues were then passed through a meat grinder and the pulpy mass obtained was used in weighed quantities.

It was found that when a small amount of liver was added to a much larger quantity of muscle in either neutral or acid hydrogen peroxide the catalytic activity of the combined mass was much greater than the total activity of the two taken separately, as measured by the volume of oxygen produced in a given time. Blood was also found to have a similar marked accelerating effect on muscle catalase, while thyroid, spleen and kidney produced only a small amount of acceleration. Pancreas and testes appeared to cause a slight retardation.

The suggestion is made that this accelerating action may be due to an internal secretion of the liver. Its presence in the blood would also account for its effect in producing acceleration.—L. G. K.

284. (MONGOLISM) Ricambio azotato nell' idiozia mongoloide e nella mixo-idiozia ed influneza su di esso della Tiroidina. (On the mongoloid idiocy and on the mixo-idiocy and of the influence on them of the thyroid treatment.) Caronia (G.) La Pediatria (Naples) 1918, **26,** 336.

The author emphasizes the difference of effect of the thyroid treatment on these two forms of idiocy, as found from personal research. The children to be examined were first kept ten days on a diet chiefly of milk, eggs, bread and cereals, so that the nitrogenous dosage was rendered very easy. Then, keeping on with the same diet, for six days the food was examined as well as the urine and the faeces. After an interval of ten more days, while the thyroid treatment was begun, there was a period of six other days, during which analysis of food, urine and faeces was made, without dropping the treatment.

For the determination of the total nitrogen Kjeldahl's method has been used for food, urine and faeces. For the urea, Morner-Syoovist's; for uric acid, Folin-Shaffer's; for ammonia, Folin-Spiro's; for the amino-acids, Henriquez-Sorensen's. The residual nitrogen (creatinine and purinic bases) was not determined.

Conclusions: (a) The nitrogenous metabolism (in the microcephalic mongoloid idiocy) is normal as regards the total retention of nitrogen, but irregular in regard to the various nitrogenous elements of the urine. There is a conspicuous retention of nitrogen and increased elimination of amino-acids. Under the influence of the thyroid the metabolism comes soon to a negative balance at the expense of the tissues, about as we find it in hyperthyroidism.

(b) In mixo-idiocy the metabolism is also irregular as regards the relations between the various elements of the urine (increased elimination of amino-acids). Under the thyroid treatment, though, the metabolism improves, showing better oxidation by diminished elimination of amino-acids and giving normal amount of the residual nitrogen and of uric acid.—G. V.

285. (ORGAN EXTRACTS.) The effects upon the gastric secretion of organic extracts. Rogers (J.), Rahe (J. M.), Fawcett (G. C.), and Hackett (G. S.). Am. Jour. Physiol. (Balt.), 1916, **39**, 345-353.

The authors were of the opinion that the equivalent of a specific gastric hormone is to be found in some substance common to many extracts which favorably affects the nutrition and consequently the activity of the gastric epithelial cells, and has some relation to their nerve supply. They accordingly tested the effects of the subcutaneous injection of organ extracts on the gastric juice of dogs in which the Pavloff isolated stomach pouch and fistula had been established.

The thyroid, or only the non-coagulable portion of an aqueous extract of the thyroid, was found to contain a substance which is an active stimulant of both gastric secretion and gastric motility. Only the "residue," or non-coagulable portions, of aqueous extracts of the parathyroid, thymus, spleen and liver were found to have a similar effect. Both the coagulable and non-coagulable portions of an aqueous extract of the pancreas are vigorous stimulants of gastric secretion. The pituitary and adrenal residues inhibit the flow of gastric secretion. All the stimulating residues seem to act upon a peripheral gastric mechanism of which the nervous system is an essential part. Injection of other organ extracts gave entirely negative results.—L. G. K.

286. (PANCREAS) Role of the pancreas in glycolysis. Lepine (R.) Rev. de méd (Paris), 1917, **35**, 289.

A protest against incriminating the pancreas alone. Certain other glands with an internal secretion are unmistakably involved in glycolysis.

287. (PANCREAS) The effects of painting the pancreas with adrenalin upon hyperglycemia and glycosuria. Kleiner (I. S.) and Meltzer (S. J.) Jour. Exp. Med. (Balt.) 1918, **27**, 647.

The authors in repeating experiments of earlier workers find that in the majority of cases painting the pancreas with adrenalin is followed by glycosuria which varies in different animals. The results of earlier experiments lead to the inference, first, that painting the pancreas with adrenalin caused a marked glycosuria and hyperglycemia, and second, that the glycosuria and hyperglycemia produced by intraperitoneal injections were of pancreatic origin. To decide this point the authors performed experiments in which the pancreas was isolated from the rest of the peritoneal cavity and found that the glycosuria produced was about one-third, and the rise in blood sugar about two-thirds that obtained by painting the unisolated pancreas. They therefore conclude, first, that the painting of the isolated pancreas produces only mild glycosuria and hyperglycemia; second, that the greater production of sugar observed after painting the unisolated pancreas cannot be of pancreatic origin, but due to the escape of adrenalin to the peritoneum. As evidence of this conclusion experiments were performed in which the adrenals were painted. The effects on sugar production was apparently as intense as that obtained by painting the unisolated pancreas. Whether the production of sugar after painting the unisolated pancreas is due to the escape of adrenalin to some definite organ covered by the peritoneum or whether the peritoneum as a whole is responsible for sugar production, it appears that, when sugar production follows intraperitoneal injections of adrenalin, it is not of pancreatic origin.—H. W.

288. (PANCREAS) Über die Bedeutung der Langerhansschen Inseln für den Kohlehydratstoffwechsel. I. Mitteilung. Das Verhalten des Blutzuckers nach Unterbindung des Ductus Pancreaticus bei Kaninchen. (The significance of the islands of Langerhans in carbohydrate metabolism. I. The retention of the blood sugar after ligation of the pancreatic duct in rabbits.) Kamimura (N.) Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo 1917, **17**, 95-126.

The author found that ligation of the pancreatic duct in rabbits resulted in complete atrophy of the parenchyma of the pancreas with the exception of the islands of Langerhans, which did not appear to show any change. No digestive disturbances resulted, and no lasting hyperglycemia or glycosuria occurred. Artificial hyperglycemias were produced in various ways (injection of adrenin and diuretine, hemorrhage and the intravenous introduction of sugar), but the animals showed no difference in their behavior towards these factors than did other normal rabbits.

These facts support the accepted belief that as long as the islands of Langerhans remain normal the carbohydrate metabolism is not interfered with in disturbances of the pancreas.—L. G. K.

289. (PANCREAS) Über die Bedeutung der Langerhansschen Inseln für den Kohlehydratstoffwechsel. II. Mitteilung. Zytolytisches Immunserum der Pancreas inseln. (The significance of the islands of Langerhans in carbohydrate metabolism. II. Cytolytic immune serum of the islands of Langerhans.) Kamimura (N.) Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo 1917, **17,** 127-136.

A serum, supposedly cytolytic to the islands of Langerhans, was prepared as follows: Saline extracts of rabbits' pancreas, the ducts of which had been previously ligatured so that only the islands of Langerhans remained in an unatrophied condition, were injected into the peritoneal cavity of a young dog. After several injections, at intervals of five to ten days, the dog was bled and the serum so obtained was injected into rabbits, some of which had previously had the pancreatic duct ligatured. Glycosuria was not produced in these animals, thus confirming the earlier work of Ssobolew and Klimenko. In some cases there was a slight increase in the blood sugar content, but the author did not attribute this to the action of a specific serum. The serum produced no noticeable pathological changes in the islands of Langerhans.
—L. G. K.

290. (PARATHYROIDS) Guanidine hydrochloride and blood-sugar. Watanabe (C. K.), J. Biol. Chem. (N. Y.), 1918, **33,** 253-265.

Paton's views on the relationship of guanidine to tetany are confirmed. It is further shown that hypoglycaemia is produced both by guanidine and removal of the parathyroids (rabbits).

291. (PARATHYROIDS) Über tödlich verlaufende Tetanie. (Fatal tetany). Stankovic (R.), Wien. klin. Woch. (Wien.), 1917, **30,** 1107-1108.

Five fatal cases in soldiers on active service are recorded. They had been exposed to privations mental and bodily. The condition is attributed to parathyroid insufficiency, and there was no evidence of compensatory action in other endocrine organs. (Med. Research Committee.)—Physiol. Abst., 1918, **3,** 130.

292. (PITUITARY) Dystrophia adiposogenitalis (Fröhlich's syndrome). Madigan (J. J.) and Moore (T. V.) Jour. A. M. A. (Chgo.), 1918, **70,** 669.

Clinical report of a case of dystrophia adiposogenitalis in a boy 10 years of age. The author believes the condition had a prenatal origin because of a hereditary taint upon the maternal side, blindness from birth, nystagmus at three or four months of age, very small optic disks and a genital aplasia of such a nature that it must have dated well back into the prenatal history of the child.—H. W.

293. (PITUITARY) The pituitary gland in epileptics. The conformation of the sella turcica (2nd paper). Munson (J. F.) Arch. Int. Med. (Chgo.), 1918, **21,** 531.

The sellas from a series of unselected epileptic subjects present a wide variation in type. The average size seems a trifle smaller than figures given for normals and the contained gland seems to weigh less. Roofing of the fossa can be seen in Roentgenograms, but contrary to impressions given by the statements of other writers, the author believes that the gland in reality is well exposed and pressure seems a remote possibility. Bony changes are present but seem to be the anomalies which might well be present in a similar series of nonepileptic cases. The author concludes that there is no characteristic change to be seen in epileptic sellas.—H. W.

294. (PITUITRIN) Uterine inertia. Titus (P.) Jour. A. M. A. (Chgo.) 1918, **71,** 890-93.

The author regards pituitrin as of relatively little use in the practice of obstetrics. Its use in the first stage of labor is regarded as indefensible. Having had three cases of hourglass contraction of the uterus with retained placenta as a result of its use in the second stage, he has come to the conclusion that its safest use is in the third stage to control uterine

relaxation and hemorrhage. He comments ironically on the free use of pituitrin by mid-wives.—R. G. H.

295. RICKETS, The modern views on the nature of. Rivista crit. de clin. med. (Firenze) by "Y" 1918, **19,** 189.

Rickets is considered as a disease of development, determined usually by dysfunction, first of one and then of all the glands of the thyro-parathyro-thymic group. The thymus lesions would alter the metabolism of calcium and cause a diminished specific activity of the cartilage cells; the parathyroids would be the cause of the spasmophilic symptoms; the exophthalmus and the lymphocytosis would be charged to a dysfunction of the thyroid.—G. V.

296. SECRETIN, Its mode of action in producing an increase in the number of corpuscles in the circulating blood. Downs (A. W.) and Eddy (N. B.). Am. Jour. Physiol. (Balt.), 1918, **46,** 209-221.

The authors have previously shown that the injection of secretin is capable of producing a marked increase in the number of erythrocytes and leucocytes in the circulating blood. Believing this increase to be due to direct stimulation of the bone marrow and lymph glands, the authors investigated the changes in the blood picture and the histological appearances of these organs after prolonged administration (8 weeks) of secretin to two rabbits. The results were compared with those obtained from two controls.

A marked increase in the leucocyte count was obtained (146.7 per cent in the third week), and a less pronounced increase in the erythrocyte count (18.5 per cent in the eighth week). At autopsy the thyroids and spleen of each of the secretin rabbits were much heavier, and the liver was slightly heavier than the same organs in the control animals. Smears and sections of the bone marrow showed that cells of all types were much more numerous in the treated rabbits. The lymph glands of the secretin animals also showed evidence of increased activity. The enlargement of the liver and spleen was attributed to the rapid accumulation in them of the debris of broken down immature erythrocytes produced by the overactive bone marrow. Alterations in the relative proportions of the different varieties of leucocytes was also found to take place and nucleated red corpuscles appeared in the blood of the secretin rabbits.—L. G. K.

297. (SEX) A demonstrtaion of the origin of two pairs of female identical twins from two ova of high storage metabolism. Riddle (O.), Jour. Exp. Zool. (Phila.), 1918, **26**, 227.

The author advances further data for a theory of sex differentiation to which he still adheres despite all cytological opposition. He states that he obtained two pairs of identical female twin doves, each pair of which was produced from a single ovum. The two yolks were of very large size, and were produced under conditions known to favor the production of females. The author claims that the fact that these two cases of identical twins were from ova of high storage metabolism and were of the female sex lends support to his theory that germinal differentiation of sex is a differential metabolism. Practically all other biologists believe that sex is determined by the chromosomes of the germinal cells.—E. R. H.

298. (SEX) A microscopic study of the reproductive system of foetal free-martins. Chapin (C. L.) Jour. Exp. Zool. (Phila.), 1917, **23**, 453. A microscopical study of the material described by Lillie in the same Journal.

In early stages the free-martin resembles the normal female embryo but it gradually comes to resemble the male in many ways. Such changes occur in the gonad in which the sex cords may resemble either the primary cords of the ovary or the seminiferous tubules of the testis. Other organs which in the sterile free-martin tend to resemble those of the male are the rete, Wolffian body and duct and the Mullerian ducts which normally form the uterus. The changes in these organs vary greatly and are believed to depend upon the amount of male internal secretions which get into the female, and upon the stage of development at which this introduction occurs.—E. R. H.

299. (SEX) Another case of gynandromorphism. Harman (M. T.) Anat. Rec. (Phila.), 1917, **13**, 425.

The author describes very briefly a cat in which the sex organs on right side consisted of an ovo-testis, uterine tube and uterus, while on the left side they were of the normal male type. The subject of gynandromorphism is discussed.—E. R. H.

300. (SEX) Studies on sex in the hermaphrodite Mollusk crepidula plana. II. Influence of environment on sex. Gould (H. N.) Jour. Exp. Zool. (Phila.), 1917, **23**, 225.

The author has shown that in a certain mollusk the colony both in natural and under experimental conditions develops all female animals until one of these reaches a point where fertilization is needed and then males develop. The males never develop under any other conditions. If the large females are removed, development of males ceases, and on the other hand males will develop from animals which have already begun to differentiate into females if the conditions are proper.—E. R. H.

301. (SEX) The free-martin; a study of the action of sex hormones in the foetal life of cattle. Lillie (F. R.) Jour. Exp. Zool. (Phila.) 1917, **23**, 371.

In cattle twins the sterile free-martin and its mate are rarely if ever monozygotic. The female zygote contains factors for both sexes. The quantitative difference between the male and female factors of the female zygote necessary for the differentiation of female characters are reduced in the free-martin by internal secretions from the male twin, and the free-martin therefore becomes a sex intergrade. In these cases the author found that the two animals receive blood from the same chorion. This permits the internal secretions from the male to be carried into the female and interfere with her normal sexual differentiation, thus producing the sterile free-martin. Different degrees of intersexuality may be produced in these free-martins. Absence of normal ovarian tissue may influence their later development by the absence of certain inhibitions normally brought about by the ovary. Sex differentiation is controllable within variable limits in certain groups of animals including mammals. The paper is well illustrated.—E. R. H.

302. (SPLEEN) Histological examination of the spleen in various infectious diseases. Kozumi (K.), Tokyo Igakkwai Zasshi, 1916, **30**, 1-30. Jap. Med. Lit. (Seoul) 1917, **2**, 2.

Contains nothing new.—L. G. K.

303. (SPLEEN) The spleen during hibernation. Mann (E. C.) and Drips (D.) Jour. Exp. Zool. (Phila.), 1917, **23**, 277.

The spleen of the gopher is congested early in hibernation. Spleenectomy does not interfere with hibernation, hence the spleen is not primarily directly concerned with hibernation.—E. R. H.

304. (TESTIS) The effects of testicular transplants upon vasomotor irritability. Wheelon (H.) and Shipley (J. L.) Am. Jour. Physiol. (Balt.), 1916, **40**, 394-400.

Previously published 1917, **1**, 482, but not included in index.

305. (THYMUS) Enlarged, in infancy. Herrick (J. F.), Surg. Gyn. and Obst. (Chgo.), 1916, **22,** 332; abstr. Arch. Ped. 1916, **33,** 792.

Enlargement of the thymus gland often causes death directly or indirectly. It is a question whether the pressure is exerted solely on the trachea or on other organs as well. The chief symptom of a thymic enlargement is a respiratory disturbance which simulates a foreign body in the trachea. This is in the form of a mild stridor both at inspiration and expiration, or it may be a very severe dyspnea with fatal termination. After fits of vomiting, coughing or crying there seems to be a few minutes of relief. Pressure on the trachea, on the vagi, and on the heart are assigned as causes of death. The diagnosis of the stridor caused by a foreign body and that caused by an enlarged thymus may be made from the gradual onset, slowly increasing difficulty, absence of foreign body in the skiagram, dullness to the side of the sternum and an enlarged gland in the X-ray shadow. It is nearly impossible to differentiate an enlargement of the mediastinal glands from one of the thymus. In an enlarged thymus, dullness is usually higher up. The thymus patient is usually well nourished, although pale and pasty looking, and without a history of tuberculosis. Slight cachexia and elevation of temperature often suggest tuberculosis in a thymus case. The author reports 6 cases, ranging in age from 4 weeks to 3 years. The X-ray treatment seems to be the most satisfactory and safest method. Extirpation is both dangerous and uncertain.—M. B. G.

306. (THYMUS) Persistence of thymus gland in relation to sudden death of adults. Taguchi (K.), Kyoto Igaku Zasshi, 1917, **14,** 1-14. Jap. Med. Lit. (Seoul) 1917, **2,** 2.

The author in a review of three cases of sudden death discusses the findings of the post-mortem examinations in their relation to forensic medicine.

The first, a woman of 23, died during anaesthesia for a curettage during which less than 15 cc. of chloroform was given. The autopsy revealed a large thymus, a mild grade of hypertrophy and fatty degeneration of the heart, and nephritis.

A 14-year-old boy was drowned and the verdict, based upon the post-mortem examination, was that the accident had occurred as a result of heart failure incident to an enlarged thymus.

A strong and well nourished man, aged 57 years, died within an hour after the administration of 1 cc. of typhoid vaccine, with symptoms of chilliness, exhaustion, headache,

dyspnoea, vomiting etc. The status thymicus was evident with characteristic findings, such as definite persistent thymus, lymphoid hypertrophy, hypogenesis of the papillary muscles of the heart, narrowing of the aorta, imperfect calcification of the xyphoid process, and costal cartilages, and a general deficiency as compared with what would be expected of a man of that age.—L. G. K.

307. (THYMUS) Status lymphaticus. Symmers (D.) Am. J. M. Sc. (Phila.), 1918, **156,** 40-58.

The paper comprises a discussion of the definition, clinical aspects and clinical signs of status lymphaticus, followed by an analysis of 249 cases seen at autopsy at Bellevue Hospital. There were 212 males and 37 females in the series. There were 118 cases which were well marked, 89 recessive and 42, border line, tending, however, toward recessive. In the 118 cases the thymus was hyperplastic in every instance. In 70 cases designated recessive the gland was "practically invisible." The only noteworthy histological change in the thymus was hypertrophy of the lymphoid follicles, but the lymph nodes often had peculiar necrotic germinal areas, especially in the subjects that had met sudden death from trivial causes. In later stages the necrotic areas were replaced by characteristic whorls of connective tissue cells. The author believes that the sudden death that is frequent in status lymphaticus is due to anaphylaxis, the sensitizing substance being derived from the necrotic lymphoid tissue. The blood vessels in a considerable number of the cases showed gelatinous alterations or hypoplasia,—a condition predisposing to cerebral hemorrhage. A high incidence of status lymphaticus was noted in cases showing emotional instability and chlorosis. For many interesting details the original should be consulted.—R. G. H.

308. (THYMUS) Über Beziehungen zwischen Thymus und Carcinom (Relationship between the thymus and carcinoma) II. Kaminer (G) and Morgenstern (O.), Biochem, Zeitsch. (Berlin), 1917, **84,** 281-331.

The authors claim to have proved that there is a close relationship between the destructive action of serum upon cancer cells and the condition of the thymus.—Physiol. Abst., 1918, **3,** 140.

309. (THYROID) A case of complete cretinism with normal mentality as the result of thyroid therapy. Hoag (W. B.). Arch. Ped. 1916, **33,** 303.

Hoag presented a girl 5½ years old, who first came under his care at the age of 3½ months. At that time, she presented the appearance of a typical cretin. At the time of reporting, she was 40 inches in height and weighed 43 pounds; she talks and plays like any other child and the mother stated that she did not then show any abnormality. Thyroid treatment had been begun at the time he first saw the child, with one quarter of a grain of thyroid extract twice daily, this being gradually increased, until for a time, when she was 4 years old, she showed signs of excessive dose, when getting 5 grains a day. She has now been getting 3 grains a day for the past few months. The case showed the results possible with thyroid medication if the case is seen early enough.—M. B. G.

310. (THYROID) Cerebral manifestations in a case of exophthalmic goitre. Heuer (G. J.) Am. J. Med. Sc. (Phila.) 1916, **151,** 339.

Heuer reports the cerebral manifestations in a case of exophthalmic goitre. This is of special interest and statistical value in that it is the first of the grave cases to be operated upon. His case is that of a man, 23 years of age. Family history unimportant. The illness was at intervals of six years' duration. The symptoms of nausea, asthenia, dyspnea, dysphagia and diplopia gradually became worse. Examination revealed the presence of a bilateral thyroid enlargement, bilateral ptosis, fixation of the globes, exophthalmos, tachycardia and extreme nervousness.

Summary of Cranial Nerve Examination: Olfactory undisturbed; diplopia; complete ophthalmoplegia externa. The pupils reacted to light. The sensory fifth nerve was unaffected, the motor markedly involved. Involvement of the seventh was shown by the mask-like face. Involvement of the remaining cranials was shown by the symptoms of dyspnea, dysphagia and dysphonia. Marked hyperesthesia was also noted.

Symptoms suggesting involvement of other glands like adrenal, hypophysis and thymus are discussed. After operation temporary improvement was noticed. Patient died from acute respiratory failure. No postmortem. A discussion of the previously reported cases indicates necessity for consideration of surgical interference, even though nerve palsies are present.—C. McP.

311. (THYROID) Development of certain types of malignant tumors of the thyroid. Wilson (L. B.) Am. Jour. Physiol., (Balt.), 1918, **45,** 573.

Malignant tumors of the thyroid are often overlooked in their early stages since many of the malignant types closely resemble benign adenomas of "fetal" type. Both benign and malignant adenomas apparently have their origin in embryonic tissue which at first consists of relatively small cells with indistinct outlines and relatively large, round or slightly oval, densely staining nuclei. These cells are irregularly arranged and are separated by scarcely discernible septa which consist essentially of thin-walled, flattened blood vessels. In the second stage the cells are arranged in cordon-like masses or long band-like platelets between which are the same sinusoid vessels. In the third stage the cordons or platelets are broken into roundish masses with the formation of acini, some of which may contain colloid. This is the most critical stage. If the acini become well developed the tumor is apt to remain benign. If the acini are irregularly or imperfectly developed the tumor is apparently more apt to become malignant, if it is not already such.

A study of the histology of supposedly benign encapsulated thyroid tumors removed at operation, in relation to these stages of development, is important for the early diagnosis of malignant conditions.—L. G. K.

312. (THYROID) Eczema due to deficient thyroid secretion in which the administration of thyroid acted as a specific. Edelman (M. H.), Arch. Ped. 1916, **33**, 932.

Edelman presented a patient, a boy, 3½ years old, who had had an eczema since the age of 4 months. He was breast fed up to the age of ten months. The eruption was of the scaly weeping type, involving the cheeks, forehead, chin, scalp, neck, shoulders, chest and upper and lower extremities. In spite of three years constant treatment by pediatrists and dermatologists, the eruption became more pronounced.

The interesting points in this case were (1) the premature grayness of the mother and her sister and their rather pasty complexions, suggestive of deficient thyroid secretion, which made it seem probable that the mother was responsible for the child's condition; (2) the persistency and extent of the eczematous condition in spite of careful dietetics and local treatment, which suggested a rather complex etiology; (3) the eczema seemed to bear no relation to the food. The improvement under thyroid extract and the regression when this medication was withdrawn, pointed to a condition of hypothyroidism. Fairly large doses of thyroid extract should be administered at first, in order to remove the results that might have been produced by privation of thyroid secretion; later smaller doses were given to maintain a normal equilibrium and pre-

vent a recurrence. The reviewer has found that in his experience, it is safer to start with small doses and gradually work up to the point of tolerance, as we do not know the degree of susceptibility of the patient toward thyroid. Edelman gives less food to these patients because of the lessened metabolic powers, as proven by Talbot in his work on the metabolism of a cretin. He gradually increases the food as they improve. Some clinicians feel that the opposite course should be pursued, that, as the thyroid may produce a loss in weight, plenty of food should be given.—M. B. G.

313. (THYROID) Effects of external temperature, morphine, quinine and strychnine on thyroid activity. Mills (C. A.) Am. Jour. Physiol. (Balt.), 1918, **46,** 329-339.

Rabbits, guinea-pigs and cats were used in this research. The animals were kept on a constant diet, and in a room maintained at a temperature of 12° to 18°C. A portion of the thyroid gland was then removed and examined microscopically, after which the animals were subjected to cold (-5° to 10° C.), heat (27° to 37°C.) or injections of quinine, morphine or strychnine. At the close of the period of treatment the remainder of the thyroid was compared with the portion previously removed. The author found that high external temperatures cause a diminished activity of the thyroids as judged by their morphological appearance, together with a slowing of the rate of growth. Low external temperatures, on the contrary, increase the thyroid activity and also seem to cause a faster rate of growth. Morphine and quinine appear to decrease the activity of the gland, probably as a result of the lessened metabolism and diminished heat production; while strychnine causes greater thyroid activity, very likely by increasing metabolism through its action on the spinal cord.—L. G. K.

314. (THYROID) Further experiments with thyroidectomy in Amphibia. Hoskins (E. R.) and Hoskins (Margaret M.) Proc. Soc. Exp. Biol. and Med. (N. Y.) 1918, **15,** 102-4.

Thyroidectomy was performed upon a large number of frog larvae, at a 6 to 8 mm. stage. After the tadpoles reached a length of about 18 mm. the growth of the operated animals was accelerated and they ultimately reached a length of 72 mm. as against 50 mm. in normal controls.

In the absence of the thyroid secretion the anterior lobe of the hypophysis underwent hypertrophy—a fact which probably accounts for the experimental gigantism that developed. The sex glands were further advanced in development in the

operated than in the control animals. This precocity is also accounted for by the hypophyseal hypertrophy. The other endocrine glands were larger in the experimental than in the control animals, but whether this was absolute or relative had not yet been determined.—R. G. H.

315. (THYROID) Goitre in children. Buford (C. G.), Surg. Gyn. and Obst. (Chgo.), 1915, **20,** 35; abst. Arch. Ped., 1916, **33,** 953.

The subject is divided by the author into (1) goiter of infancy under one year of age, and (2) goitre of childhood, one year to adolescence, (3) goitre of adolescence. Almost 90 per cent of the older cretins show goiter. Certain results can be brought out of cretinism by early thyroid feeding. It is possible that in some the gland is delayed in development and in the performance of its duties, and if not fed thyroid these children may be permanently damaged. Goiter among newly-born children seems rare to the author, who has seen one case in a baby six days old. Brooks reports several cases which have appeared about the second day after birth and says that they invariably disappear.

In the goiter of children there is almost uniformly an area well defined in the gland. About 9 in 10 show the lesion in the right lower pole of the right lobe. As the mass enlarges, it encroaches upon the median line. In early cases the tumor is hard and well defined. In the more advanced cases the induration is more distinct and the anterior border more rounded. In the still more advanced cases, the tumor is rotund, outlines definite, consistency firm or fluctuating, neck enlarged and capsulation quite complete. When these encapsulated masses are removed they are found to be benign adenomas. These types of goiters are often associated with diseased tonsils.

The symptoms associated are largely proportionate to the apparent changes of the gland. The patients are usually below standard in health and stature. Muscles are soft and posture drooping; fatigue comes easily. They are languid, do not enjoy play and are irritable. The hair usually has a gritty feeling. Moist cold hands with a coarse or fibrillary tremor limited to the hands is sometimes characteristic. The pulse ranges from 80 to 120.

The treatment is thyroid feeding. The goiter may disappear in six weeks under treatment. Adolescent goiter usually appears as a bilateral affection. When unilateral the enlargement is usually in the right lobe. When there is no suggestion of hyper-thyroidism, iodin or thyro-iodin should be given.—M. B. G.

316. (THYROID) Goitre in pregnancy. Watson (L. F.) Jour. A. M. A. (Chgo.) 1918, **71,** 875-77.

As a result of a consideration of the literature and of his own cases, a few of which are cited, the author concludes that "pre-existing goitre, either simple or toxic in type, is usually aggravated by pregnancy. The symptoms and growth of hyperplastic goitre in pregnancy can usually be controlled by quinine and urea injections into a portion of the thyroid gland. Should symptoms progress in spite of conservative measures, a rapid delivery is indicated. Operation on the thyroid is indicated to relieve pressure symptoms of solid goitres. Cystic goitre may be promptly relieved by quinine and urea injections. Pregnant women with subthyroid conditions should receive iodids or thyroid throughout gestation." In the author's experience untoward results have not followed the quinine and urea treatment. He uses only small doses (5 to 10 minims) at one to three-day intervals.—R. G. H.

317. (THYROID) Goitre in the southeast. Jones (E. J.), Jour. A. M. A. (Chgo.), 1918, **71,** 712-15.

The incidence in the Southeast of the several types of goiter departs in no significant way from the incidence in other areas where thyroid troubles are not definitely endemic. Sixty per cent of all goiters are listed as nontoxic; excluding from consideration the symptomless goiters of puberty, 64 per cent of the nontoxic goiters are adenomas. Goiter in this territory is relatively rare; the colored race exhibits less tendency to a pathologic condition of the thyroid than does the white race; men are less frequently affected than published figures indicate; the occurrence of nontoxic goiters in families is suggestive, but not significant; no particular water supply is under suspicion. There appears in this series no significant relation between pelvic disease and a pathologic condition of the thyroid. Maximum double resection in diffuse enlargements is wise.—Author's summary.

318. (THYROID) Heteroplastic grafts with thyroid from cases of Graves' disease. D'Agata (G.) Lo Spirem. (Firenze) 1918, **71,** 392-404.

Transitory functional alterations were observed. These were ascribed to the absorption and entrance into the circulation of substances arising in the transplanted thyroid tissue.—Chem. Abst. **12,** 1317.

319. (THYROID) La crosse de l'aorte dans le goitre exophthalmique. Folley (C.), Soc. d. Biol. (Paris), 1918, **166,** 311-312.

Dilatation of the aorta is an early and constant symptom of exophthalmic goitre.—Physiol. Abst., 1918, **3,** 137.

320. (THYROID) Nervous and mental symptoms in exophthalmic goitre. Barker (L. F.), Jour. A. M. A. (Chgo.), 1918, **71,** 327-29.

A general discussion of the topic not lending itself to abstracting.—R. G. H.

321. (THYROID) Sounds in exophthalmic goitre. Reisman (D.) Jour. A. M. A. (Chgo.) 1916, **66,** 1381.

Of clinical interest. Reisman reports having heard a bruit, synchronous with the heart beat, over the eyeball in a case of exophthalmic goitre. The sound is heard when the bowl of the stethoscope is placed over the eye, the lid being closed. The sound is not constant and occurs also in aortic insufficiency. It has been reported previously by Snellen, Donders, Hunter, Carrington and Drummond.—C. McP.

322. (THYROID) Sulla diagonsi e cura degli stati ipertiroidei. (The diagnosis and treatment of hyperthyroidism.) Pisani, from Maranon. Revista Ibero-Am. de cien. med. (Madrid) June, 1917. Rivista crit. di clin. med. (Firenze) 1918, **19,** 58.

According to Maranon several types of hyperthyroidism are found classed in regard to their different functional manifestations:

(a) Cardio-vascular; (b) nervous type (the neuroses from fear are almost always forms of hyperthyroidism); (c) diabetic type where, besides some thyroid symptoms, the glycosuria depends more on the nervous influence, than on the diet; (d) tubercular type (where, though, a nice separation from actual tuberculosis is not always feasible); (e) digestive type (hyperchloridria, diarrhea, etc.); (f) Kraus's cardiac goiter.

The different aspects are caused by peculiarities of the thyroid secretion and still more by the patient's constitution and, finally by the conditions of the other endocrine glands. This last statement is found true in about 95 per cent of cases.

The therapy of any of such forms must be mostly medical; surgical only when the medical fails. After quoting the various medical treatment as carbohydrates, climate, cold applications, electricity (the author would recommend the galvanofaradic) and radiotherapy (rather doubtful), he seems to recommend calcium, phosphorous and atropin. He disclaims any benefit from iodin treatment, which he would allow only

very seldom and with the utmost caution. Coming to the opotherapeutic preparations, he declares the thyroid treatment uncertain and often dangerous; if chosen, very small doses are to be given. He does not find justified the use of thymus, as exciting the thyroid. The hypophysis is good as cardiotonic. Parathyroid preparations are only symptomatic remedies for the tachycardia. Pancreas preparations give negative results.

In conclusion he advises ovarian therapy in some cases determined by ovarian insufficiency; suprarenal in cases of decided hypotension; the pluriglandular combined according to the needs, and finally, in acute cases, he insists on antithyroid sera.—G. V.

323. (THYROID) Temporary loss of voice following thyroidectomy. Guthrie (D.) Jour. A. M. A. (Chgo.), 1918, **71,** 715-18.

The causes of temporary loss of voice are given by the author as follows: (1) Trauma to the inferior recurrent laryngeal nerves; (2) trauma to the larynx and trachea; (3) syphilis; (4) hysteria. An operative technique for the avoidance of the first two is described and illustrated. The suggestion is offered that all patients who have insignificant goitres but complain of interference with speech be submitted to a Wasserman test. The significance of hysteria in these cases and methods of treatment of the condition are discussed. The need of the assistance of skilled anesthetist is especially emphasized. —R. G. H.

324. (THYROID) The active constituent of the thyroid. Kendall (E. C.) Jour. A. M. A. (Chgo.) 1918, **71,** 871-72.

A somewhat fuller treatment of the topic has been published by the author in Endocrin., 1918, **2,** 81.—R. G. H.

325. (THYROID) I. The blood sugar in thyroid and other endocrine diseases. Janney (N. W.) and Isaacson (V. I.) Arch. Int. Med. (Chgo.) 1918, **22,** 160.

Experiments upon dogs demonstrate that hypoglycemia results from hypoendocrine function in the case of the thyroid gland, where hyperglycemia regularly develops after thyroidectomy. This finding, therefore, offers an explanation for the low blood sugar value observed in myxedema, cretinism, Addison's disease, pituitary diseases and other less clearly defined endocrine disturbances such as muscular dystrophy. The increased glucose tolerance, as determined by testing the urine in diseases of the ductless glands, is probably best explained as

due to the hypoglycemia present in these conditions. Experimentally it was found that the assimilation of glucose from the blood was delayed following thyroidectomy. The same changes were demonstrated in cretinism, exophthalmic goiter, and hypophyseal disease. Determinations of the fasting blood sugar value and the glucose tolerance are considered by the authors as useful procedures in the diagnosis of endocrine diseases.—H. W.

326. (THYROID) II. The influence of thyroidectomy and thyroid diseases on protein metabolism. Janney (N. W.) and Isaacson (V. I.) Arch. Int. Med. (Chgo.), 1918, **22**, 174.

This paper presents the results of experimental work upon dogs and clinical patients relative to urinary nitrogenous substances following thyroidectomy. No selective action of the thyroid was observed on urea and ammonia, but the urinary purines decreased following thyroidectomy and were greatly increased in experimental hyperglycemia. There was also noted a tendency to a low purine excretion in the cretin and a high excretion in a case of exophthalmic goiter. Creatinin was not found to be increased in the urine even when large amounts of body tissue were being broken down in experimental hyperthyroidism. Therefore it appears that creatinin is not a direct product of protein catabolism and also, that creatinin metabolism is independent of thyroid influence. The experimental work does not support the view that any marked diminution of nitrogen excretion follows thyroidectomy in animals. Also, cretins fail to show a particularly low output of nitrogen. Such findings lead to the belief that the decrease in the protein breakdown, observed by others in cretin metabolism, is due rather to an inability for growth and repair of tissues to take place.—H. W.

327. (THYROID) III. Studies in thyroid therapy: the effects of the thyroid hormone as determined by clinical, metabolic and dietetic investigations. New points of view on thyroid function in health and disease. Janney (N. W.) Arch. Int. Med. (Chgo.) 1918, **22**, 187.

The author describes therapeutic experiments with Dr. Kendall's thyroid preparation, the effects of thyroid administration on metabolism, and of diet in thyroid diseases. The effects of thyroid preparations on the protein metabolism were followed over continued periods, with estimations of the nitrogen intake, output and balance. The results of a series of experiments on control individuals indicate that the normal

organism is more sensitive to minute doses of thyroid than had generally been supposed. The earliest observable effect was a tendency for a positive nitrogen balance to diminish, this condition being at times associated with a loss of weight. Hence, the smallest amount of hormone added from without, in the case of normally functioning thyroids, tends to cause nitrogen loss. In the cretin identical amounts of thyroid which caused nitrogen loss with or without toxicity in normal individuals led to a large gain in nitrogen accompanied with improvement in the clinical symptoms. "This effect was so delicate that the nitrogen balance could be used as a gauge of the correctness of the dosage. Therefore, the therapeutic action of the thyroid is anabolic and constructive." In exophthalmic goiter the hormone was less satisfactory. However, the author believes that the symptoms of toxicity exhibited on the doses employed do not indicate that the hormone acts differently from other thyroid preparations in these toxic cases. In spite of the known tendency to nitrogen loss in exophthalmic goiter, the nitrogen balance became increased when 0.02 mg. of the hormone iodin was administered.

Diets supplying increased calories do not improve the clinical condition of cretins, since only a reduced amount of food can be assimilated by the untreated subject. Cretins should therefore be maintained on a liberal diet, and not subjected to forced feeding. In the dietetic treatment of exophthalmic goiter neither a high protein nor a high carbohydrate diet is followed by as good results as is a mixed diet of adequate caloric value.

From the results of his own work and a critical review of the literature the author is led to doubt the adequacy of the "hyperthyroid theory" of exophthalmic goiter. A tentative theory is put forward which assumes that the result of the premature discharge of a "hypothetical toxic intermediary product" would result in an impoverishment of the gland of the thyroid hormone. Such a theory would explain the fact that in Graves' disease goiters are poor in iodine, and especially in the Alpha-iodine proteins. The decreased production of the normal hormone due to this cause would tend to be accompanied or followed by signs of thyroid insufficiency. Thus the deficiency symptoms can be accounted for; also the concomitant occurrence of hypothyroid and hyperthyroid symptoms, and the tendency of exophthalmic goiter patients to develop myxedema.

Such considerations indicate first, that the depressed nitrogen excretion in cretinism is not due to absence of stimulatory effect, but rather to the failure of normal repair and growth

processes which are controlled by the thyroid; second, that a gain, not a loss, of nitrogen is a result of the therapeutic action of the thyroid, and that a loss of nitrogen is due to a toxic action of the gland.—H. W.

328. (THYROID) The energy of metabolism in a cretin. Talbot (F. B.) Am. Jour. of Obst. (N. Y.) 1916, **74,** 549.

This subject was a typical cretin, three years and eight months of age, and was studied in the respiratory chamber devised by Benedict. They found his basal metabolism per kilo body weight was 40½ calories, and per square meter of body surface, 898 calories per twenty-four hours. In the absence of normal data in children of the same age this metabolism was compared with that of a normal eight months' baby and a normal ten months' baby. The metabolism of the cretin was decidedly lower than that of the two normal babies. Unfortunately, results after treatment with thyroid have not been sufficiently accurate to use. These results were consistent with those of Magnus Levy and the more recent work of Dubois. The practical application of these findings is that the cretin requires less food than children with sufficient thyroid activity and that after treatment with thyroid extract would require more food than before treatment.—W. H.

329. (THYROID) The influence of thyroid preparations given parenterally on nitrogenous metabolism and on the blood in myxedema. Peillon (G.) Mitt. Grenzg. Med. Chir. (Jena), 1916, **29,** 245-69; Physiol. Abst. **1,** 489.

Thyroid preparations increase the N metabolism, especially when given parenterally. The effect is proportional to the I content of the preparations. Another effect is an increase of leucocytes and a decrease of lymphocytes.—Chem. Abst., 1918, **12,** 1487.

330. (THYROID) The influence of iodothyroglobulin and thyronucleoprotein on nitrogenous metabolism in myxedema and Graves' disease. Courvoisier (H.), Mitt. Grenzg. Med. Chir. (Jena), 1916, **29,** 70-84; Physiol. Abst. **1,** 489.

In myxedema, thyronucleoprotein causes N retention, and the blood picture characteristic of the disease is exaggerated; iodothyroglobulin increases the output of N, and the blood picture returns to normal. If both preparations are given together, the effect of the thyronucleoprotein comes first, followed by that of the thyroglobulin. In Graves' disease, iodothroglo-

bulin increases the excretion of N, and renders the blood picture worse; thyronucleoprotein causes retention of N and does not affect the blood.—Chem. Abst., 1918, **14,** 1487.

331. (THYROID) The effect of thyroid preparations on metabolism and the blood picture in myxedema and cretinism. Lanz (W.), Mitt. Grenzg. Med. Chir. (Jena), 1917, **29,** 285-308; Physiol. Abstracts **1,** 489.

In hypothyroidism, iodothyroglobulin causes a negative N balance. The P-containing constituent (nucleoprotein) has no action. Activity is proportional to the I content.—Chem. Abst. 1918, **14,** 1487.

332. (THYROID) The action of thyroid preparations in thyroid disease. Kocher (A.), Mitt. Grenzg. Med. Chir. (Jena), 1918, **29,** 309-19; Physiol. Abstracts, **1,** 489.

A commentary on the work described in the preceding abstracts, which was carried out under K.'s supervision.—Chem. Abst. 1918, **14,** 1487.

333. (THYROID) The principles of thyroid surgery. Mayo (W. J.), Jour. A. M. A. (Chgo.), 1918, **71,** 710-12.

A general paper not suitable for abstracting.—R. G. H.

334. (THYROID) The prognosis of exophthalmic goitre. Stanton (E. MacD.) Am. Jour. Med. Sc. (Phila.), 1918, **156,** 369-75.

This is a study based on the analysis of some 1600 cases in the literature. The results are tabulated in a novel way, showing the number of years of life after operation, years traced, years cured or improved, etc. In other words the time factor is introduced systematically. The author's conclusions are quoted:

"Removal of a portion of the thyroid gland of patients suffering with exophthalmic goitre produces a profound immediate effect noticeable within a few days of the operation and characterized chiefly by an improvement in the subjective symptoms of discomfort felt by the patient, but also accompanied by a marked fall in the pulse rate, a diminution of the tremor and an increase in weight.

"This initial improvement, however, seldom amounts to a cure. The exophthalmos usually persists for months or years. The heart remains irritable, the pulse becoming rapid with

exertion or excitement and at irregular periods we may expect acute exacerbations of toxic symptoms, which may alarm both the patient and the surgeon.

"The general tendency is, however, toward improvement rather than recurrence, and after a variable length of time a few patients may have failed to improve or even have grown worse; but the great majority, I believe about 80 per cent, will have continued to improve, so that finally practically all traces of their former trouble disappears.

"It is useless for the surgeon to claim that there is no medical side to the treatment of exophthalmic goitre. After five or six years there is probably little to choose between the medical and surgical end-results as regards either the mortality or the condition of the surviving patients.

"Patients surviving operation have been promptly relieved of the more distressing subjective symptoms, and the majority of them will have been able to return to their normal work in about half the time that it would have taken them to reach the same state of improvement under medical treatment. Against this is the primary mortality which must always accompany operations for exophthalmic goitre unless we are to deny the chance of operative relief to many cases most in need of the relief.

"In the future the man best able to treat exophthalmic goitre will be the one who has developed the judgment necessary to enable him to select the treatment, medical or surgical, best adapted to the individual case. The decision will depend upon many factors, not the least of which will have to do with the social condition of the patient, and whether she or he can afford the time and expense necessary for the prolonged rest required to effect a medical cure."—R. G. H.

335. (THYROID) The relationship of the so-called idiopathic cardiopathy to exophthalmic goiter. Symmers (D.) Arch. Int. Med. (Chgo.), 1918, **21**, 337.

This paper should be of special interest to the clinician and pathologic anatomist. The author describes six cases of so-called idiopathic cardiopathy, all of which showed naked eye changes in the thyroid gland. In five cases the thyroid was considerably enlarged, in one case diminished in size. From a thorough study of these cases the author concludes that the symptomatology of the condition described by clinicians as thyrotoxic cardiopathy is identical with the symptomatology of the lesions familiarly known among pathologic anatomists as idiopathic dilation and hypertrophy of the heart. Such cases,

are therefore believed to constitute a clinical and pathological entity and not an atypical form of exophthalmic goiter.—H. W.

336. (THYROID) Vincent's syndrome (clinostatic bradycardia, hypotension and acrocyanosis). Marchetti (G.) Rivista crit. di clin. med. (Firenze) 1918, **19,** 296.

By clinostatic bradycardia the author means the difference in number of the pulsations from standing to reclining position, which, instead of being 8-9, may be 15-20-25-30. Lying down the patient's pulse count goes down to 58-53-40 a minute. The hypotension is more accentuated in a standing position. The acrocyanosisis shown by damp, cold, cyanotic hands and feet as well in winter as in summer. The syndrome is found in young people who show insufficiency of the thyroid. The thyroid treatment with KI or Na I brings forth rapid, constant and lasting benefit. The ovarian treatment may be a valuable coadjuvant in some cases.—G. V.

337. (THYROID EXTRACT) Spasmus nutans. Gordon (M. B.) N. Y. Med. J. 1916, **104,** 453.

The writer gives a clinical report of three cases of this type of functional hyperirritability of childhood. In all three instances, he found rickets to be associated and probably an etiological factor. He administered thyroid extract in two of the cases with good results.—M. B. G.

338. (THYROID EXTRACT) The treatment of rickets. Gordon (M. B.) N. Y. Med. J. 1916, **103,** 696.

In addition to general, hygienic and corrective dietetic measures, the writer states that in the line of remedial agents, the use of thyroid extract has proven efficacious in his experience. This may be started with one-eighth grain doses twice daily and gradually increased to as much as one grain three times a day. The child should be watched for untoward symptoms, but to avoid these, the extract is given ten days on and ten days off. In the interim, the elixir of the glycerophosphates of lime and soda in half dram doses two or three times a day is given. This may be changed at times to the compound syrup of hypophosphites. In other cases, especially in those associated with convulsions, thyroid extract, one-eighth grain, with calcium lactate, two grains, two or three times a day has proved beneficial, the thyroid being increased gradually to one grain three times a day.—M. B. G.

339. (THYROID HYPOPHYSIS) The influence of thyroid and hypophysis removal upon general body growth and upon the development of the limbs of Rana and Bufo. Allen (B. M.) Anat. Rec. (Phila.) 1918, Vol. 14.

From a large number of tadpoles of these two types, the thyroid gland was removed, while from others the anterior lobe of the hypophysis was removed. In both species the removal of either of these glands caused the development of the limbs to be very greatly retarded from the time of their first appearance. In Rana pipiens removal of the hypophysis caused a marked retardation of general body growth, to which a corresponding retardation of limb growth was closely correlated. These tadpoles finally attained a total length of 48.9 mm. and a hind leg length of 1.48 mm. This was in marked contrast to the continued growth of the general body dimensions and of corresponding hind-limb length in thyroidless tadpoles of this species. In Bufo lentiginosus the results were not so divergent. The removal of the anterior lobe of the hypophysis early caused a color change from black to golden yellow. The absence of either gland caused retardation in limb development. Tadpoles deprived of the anterior lobe of the hypophysis reached a length far in excess of that reached in normal tadpoles. The limbs grew to about three-fifths the length attained in normal toads at metamorphosis. Thyroidless specimens grew somewhat larger than the foregoing, reaching a length of trunk almost twice that of normal toads at metamorphosis, while the hind legs and forelegs grew to a length greater than found in normal toads at metamorphosis. In none of the operated tadpoles did the fore limbs break through the skin.—E. R. H.

340. (THYROID, PARATHYROID). The effect of thyro-parathyroidectomy on the blood coagulation time in the dog. Simpson (S.) and Rasmussen (A. T.). Am. Jour. Physiol. (Balt.), 1916, **40**, 148.

Data elsewhere reported. See abstract in this journal, 1917, **1**, 350.—L. G. K.

341. (THYROID, PARATHYROID) The effect of thyro-parathyroidectomy on heart and circulation. Part 1. Action on nervous control of heart. Burns (D.) and Watson (A. McL.), Journ. Physiol. (London), 1918, **52**, 88-94.

The authors conclude from previous work that the symptoms of tetania-parathyreopriva (especially the increase in pulse-rate) are due to the presence of excessive amounts of guanidin and in this research have investigated the action of

the salts of guanidin on the vago-cardiac inhibitory mechanism.

The carbonate hydrochloride, and lactate salts of guanidin were injected in doses ranging from 50 mgms. to 1200 mgms. per kilo. The minimal current necessary to inhibit the heart through the vagus was determined in a normal animal before and after injection. The current was raised in the latter case. A solution of calcium lactate restored the inhibitory mechanism to normal.

The minimal current was then determined in an animal before and and after parathyroidectomy with the same result as above, the difference being only in degree.

The guanidin effect is first a nicotine action, i. e., on the synapse; after more extensive application, an atropine action, i. e., on the terminal ganglia.—W. E. B.

342. (THYROID THYMUS) The effects of the ductless glands on the development of the flesh flies. Kunkeld (B. W.) Jour. Exp. Zool. (Phila.), 1918, **26**, 255.

The author found that thyroid fed to fly larvae, apparently hastened maturity slightly in most cases, that the larvae were shorter than normal. His results with thymus feeding were essentially negative. His results with thyroid are in line with the well established theory that thyroid feeding stimulates metabolism.—E. R. H.

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